Incidence, microbiology and outcomes in patient hospitalized with infective endocarditis

ORIGINAL ARTICLE

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Abstract: 350
Word count: 3,573
Tables & Figures: 5
References: 45

Abstract

Background: Despite improvements in management, infective endocarditis remains associated with high mortality and morbidity. We describe temporal changes in the incidence, microbiology and outcomes of infective endocarditis and the impact of changes in national antibiotic prophylaxis guidelines on incident infective endocarditis.

Methods: Using a Scotland-wide, individual-level linkage approach, all patients hospitalized with infective endocarditis from 1990 until 2014 were identified and linked to national microbiology, prescribing and morbidity and mortality datasets. Linked data were used to evaluate trends in the crude and age- and sex-adjusted incidence and outcomes of infective endocarditis hospitalizations. From 2008, microbiology data and associated outcomes adjusted for patient demographics and comorbidity were also analyzed. An interrupted time series analysis was performed to evaluate incidence before and after changes to national antibiotic prophylaxis guidelines.

Results: There were 7,638 hospitalizations (65±17 years, 51% females) with infective endocarditis. The estimated crude hospitalization rate increased from 5.3/100,000 (95% confidence interval [CI] 4.8-5.9) to 8.6/100,000 (95% CI 8.1-9.1) between 1990 and 1995 but remained stable thereafter. There was no change in crude incidence following the 2008 change in antibiotic prophylaxis guidelines (relative risk of change 1.06, 95% CI 0.94-1.20). The incidence rate in patients >80 years doubled from 1990 to 2014 (17.7/100,000 [95% CI 13.4-23.3] to 37.9/100,000 [95% CI 31.5-45.5]). The predicted 1 year age- and comorbidity-adjusted case fatality rate for a 65 year-old patient decreased in women (27.3% [95% CI 24.6-30.2] to 23.7% [95% CI 21.1 to 26.6]) and men (30.7% [95% CI 27.7-33.8] to 26.8% [95% CI 24.0-29.7]) from 1990 to 2014. Blood culture data were available from 2008 (n=2,267/7,638, 30%), with positive blood cultures recorded in 42% (950/2,267). Staphylococcus (403/950, 42.4%) and streptococcus (337/950, 35.5%) species were most common. *Staphylococcus aureus* and enterococcus had the highest 1 year mortality (adjusted odds ratio 4.34 [95% CI 3.12-6.05] and 3.41 [95% CI 2.04-5.70], respectively).

Conclusions: Despite changes in antibiotic prophylaxis guidelines, the crude incidence of infective endocarditis has remained stable. However, the incidence rate has doubled in the elderly. Positive blood cultures were observed in less than half of patients, with *Staphylococcus aureus* and enterococcus bacteremia associated with worse outcomes.

Clinical perspective

What is new?

- Several studies have recently evaluated the changing epidemiology of infective endocarditis before and after guideline recommendations. These studies have predominantly studied the incidence, rather than the outcomes or microbiology, of infective endocarditis.
- Using a national, individual patient-level linkage approach, we describe the changing age- and sex-stratified incidence and outcomes of infective endocarditis in Scotland between 1990 and 2014.
- We further describe temporal changes in patient characteristics and microbiology based on positive blood cultures associated with infective endocarditis.

What are the clinical implications?

- The crude incidence rate of infective endocarditis hospitalizations increased from 1990 to 1995 but has remained relatively static thereafter with both short- and long-term adjusted case fatality rates showing a steady decrease over the last 25 years.
- The majority of patients with endocarditis in our cohort did not have positive blood cultures and in those with positive microbiology, staphylococcus and enterococcus conferred the highest risk for all-cause mortality.
- Changes in guidelines regarding antibiotic prophylaxis in the United Kingdom have not resulted in a significant change in incident cases of infective endocarditis.

Introduction

Despite recent improvements in management, infective endocarditis remains associated with high morbidity and mortality.[1, 2] Over the last few decades, several factors have impacted on both the incidence and outcomes of infective endocarditis. The population at-risk of infective endocarditis has increased due to changes in population demographics, a rise in the use of implantable cardiac devices, an increase in the number of patients undergoing hemodialysis for end-stage renal failure, and a greater number of patients with congenital heart disease surviving to adulthood.[3] Changes in national guidelines regarding the use of antibiotic prophylaxis for prevention of infective endocarditis[4,5] have also been implicated in the apparent increase in the incidence of infective endocarditis.

Several studies have recently evaluated the changing epidemiology of infective endocarditis, predominantly incidence,[6] before and after guideline recommendations.[4, 7-10] Fewer studies have evaluated microbiological causes and associated outcomes of endocarditis.[11, 12] Using a national linkage approach, we describe the changing age- and sex-stratified incidence and outcomes of infective endocarditis in Scotland over the last 25 years and the impact of changes in national guidelines on antibiotic prophylaxis. With the availability of a national microbiology surveillance registry from 2008 onwards, we additionally describe the microbiology of infective endocarditis based on positive blood culture data in a sub-group of infective endocarditis hospitalizations between 2008 and 2014.

Methods

The data, analytic methods and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure. However, these individual-level data are available via application to NHS Information Services Scotland.

Study design and data sources

We conducted a consecutive retrospective individual patient linkage study across multiple national databases ***(Supplementary figure 1)***. In brief, Scottish hospital discharge codes were used to identify patients hospitalized with infective endocarditis. All episodes for patients aged ≥20 years admitted between 01/01/1990 and 31/12/2014 identified as infective endocarditis were linked to the national hospitalization register (Scottish Morbidity Record 01) in Scotland. Incident cases of infective endocarditis identified from the national hospitalization register between 01/01/2008 and 31/12/2014 were additionally linked to positive blood culture data derived from individual patients derived through linkage with the national microbiology surveillance database (Electronic Communication of Surveillance in Scotland) ***(Supplementary text 1).***

Participants

Incident episodes of infective endocarditis were identified from hospital inpatient records using the International Classification of Diseases (ICD) codes ***(Supplementary text 2)***. Based on our validation exercise, only patients with a diagnostic code for endocarditis in the first two positions were included ***(Supplementary text 3)***. A five year look-back period minimized the risk of recurrent episodes of infective endocarditis from being misclassified as incident cases (***Supplementary text 4***).

Covariates

For each patient hospitalization, we extracted age at hospitalization, sex, comorbidity and socio-economic status. Socio-economic status was assessed via a national area-based measure of deprivation, the Scottish Index of Multiple Deprivation (SIMD). The SIMD is measured in quintiles with the fifth quintile being least deprived. In brief, SIMD identifies small geographical regions (each region related to postal ['zip'] code and corresponding to approximately 750 residents) of material deprivation based on information derived from seven domains (income; employment; health; education, skills and training; geographic access to services; crime; and housing).[13] Scores from each domain (which are themselves weighted according to their relative importance) are combined into an overall score, which in turn allows that area to be ranked. Scores and ranks based on SIMD have been used extensively in published epidemiological research from Scotland,[14,15] including guiding primary prevention in Scotland.[16] For our study, every patient enrolled in our cohort was assigned a SIMD quintile based on their ***individual*** SIMD rank at the time of their index admission.

Patient comorbidities were defined using established ICD codes based on previous hospitalizations and procedures using a five year look-back period. For every case of infective endocarditis during the 25 year period from 1990 until 2014, we extracted the following comorbidity data: (history of) myocardial infarction, cerebrovascular disease, heart failure hospitalization, implanted cardiac device and cardiothoracic surgery ***(Supplementary text 2)***. From 2009 onwards, prescribing data were used to provide additional comorbidity classifications based on dispensed drugs ***(Supplementary text 5)***.

Statistical analysis

Baseline characteristics of all hospitalizations were summarised by 5 calendar year groups from 1990 to 2014 and in single calendar year groups from 2008 onwards. Baseline characteristics were also summarised by blood culture detail. Incident hospitalizations were summed by calendar year, age and sex. Mid-year population estimates for the general population in Scotland, stratified by age and sex, were obtained from National Records of Scotland. For people without incident infective endocarditis, person-time not at risk (attributable to incident infective endocarditis events) was also summed by the same stratifying variables. Within the levels of these stratifying variables, person-time for people with no infective endocarditis was obtained by subtracting the infective endocarditis person-time from the mid-year population estimates ***(Supplementary text 4)***. Outcomes consisted of mortality, stroke, heart failure and valve surgery at 30 days and 1 year following the index presentation.

Modelling

Generalized additive models were used to estimate trends in incidence and outcomes of infective endocarditis. For incidence rates, log link and Poisson error distribution were used with a scaling factor (quasi-Poisson) to allow for overdispersion. Incidence rates per annum were generated for the whole population and stratified by sex and age. For outcomes, 1 year mortality was the primary outcome and year of admission as the primary explanatory variable adjusted for age, sex, comorbidity and deprivation. For both estimation of trends in the incidence rates and outcomes of infective endocarditis, models were fitted using non-parametric smooth terms (penalized thin plate regression splines) for the year of admission. For the analysis of the association between 30 day and 1 year mortality and microbiology, logistic regression models were constructed adjusted for age, sex, deprivation and comorbidity.

An interrupted time series analysis[17] was used to evaluate the incident rates of infective endocarditis before (2001 to 2007) and after (2008 to 2014) the introduction of new antibiotic prophylaxis guidelines from the National Institute of Health and Care Excellence (NICE) ***(Supplementary text 6)***.[18] A sensitivity analysis was also performed to evaluate the effect of restricting the cohort to the first diagnostic coding position. Statistical analysis was performed in R, Version 3.5.1 (Vienna, Austria).

Results

Across 7,513 individual patients, there were 7,638 hospitalizations (mean age 65±17 years, 51% females) with incident infective endocarditis from 1990 to 2014 in Scotland ***(Table 1; Supplementary table 1).***

The estimated crude rate of hospitalization increased from 5.3 per 100,000 (95% confidence interval [CI] 4.8 - 5.9) to 8.6 per 100,000 (95% CI 8.1 - 9.1) between 1990 and 1995 but remained stable thereafter with the incident rate in 2014 of 8.1 per 100,000 (95% CI 7.5 - 8.9) ***(Figure 1a; Supplementary table 2)***. Similar relative changes were seen in the incidence of infective endocarditis in our sensitivity analysis restricting the cohort to the first diagnostic code position ***(Supplementary figure 2)***. Estimated rates comparing men and women also appeared similar up until 2003, but appeared to diverge thereafter ***(Supplementary figure 3; Supplementary table 2)***.

When stratified by age, patients >80 years showed a marked increase in the incidence of infective endocarditis rising from 17.7 per 100,000 [95% CI 13.4 - 23.3] in 1990 to 37.9 per 100,000 [95% CI 31.5 - 45.5] in 2014 ***(Figure 1b; Supplementary table 3)***. In contrast, in the 60-79 year age group, the estimated rate was 11.5 per 100,000 (95% CI 10.1 - 13.2) in 1990 peaking at 20.6 per 100,000 (95% CI 19.2 - 22.0) in 1996 before steadily decreasing to 12.6 per 100,000 (95% CI 11.1 - 14.3) in 2014. In the younger age groups, the incident rates of endocarditis appeared relatively unchanged ***(Figure 1b; Supplementary table 3)***. There was no change in the incident rate of infective endocarditis following implementation of NICE guidelines on antibiotic prophylaxis (relative risk of change 1.06, 95% CI 0.94 - 1.20, p=0.420) ***(Figure 2)***.

During the study period, 32% (2,426/7,638) of patients admitted to hospital with infective endocarditis died within one year of admission. Both age and sex influenced 1 year mortality, adjusted for deprivation and comorbidity ***(Supplementary table 4)***. Age-adjusted and sex-stratified predicted case fatality rates are shown in ***Supplementary figure 4*** *and* ***Supplementary table 5***. For a 65 year-old female, the predicted risk of one year mortality reduced from 27.3% in 1990 (95% CI 24.6% - 30.2%) to 23.7% (95% CI 21.0% - 26.6%) in 2014. Similarly, for a 65 year-old male, the risk of one year death fell from 30.7% (95% CI 27.7% - 33.8%) to 26.8% (95% CI 24.0 - 29.7%). Past history of cerebrovascular disease (adjusted odds ratio [OR] 1.28, 95% CI 1.07 - 1.49), heart failure hospitalization (OR 2.09, 95% CI 1.96 - 2.22) and deprivation (OR 0.92, 95% CI 0.88 - 0.95 per unit increment in rank; rank 1 assigned as being most deprived and rank 5 as least deprived) were also associated with a higher risk of death at one year.

Data on incident cases of infective endocarditis were available from 1990 to 2014. However, positive blood culture data were also available from 2008 until 2014. As such, the population with blood culture microbiology linkage consisted of 30% (2,267/7,638) of all hospitalizations ***(Table 2)***. Positive blood cultures were recorded in 42% (950/2,267) of hospitalizations with the majority of the remainder being culture negative (defined as individuals in whom blood cultures yielded no organism or in whom no cultures were performed).

From our validation exercise, 12.5% of patients with a clinical diagnosis of infective endocarditis did not have blood cultures taken ***(Supplementary text 3)***. At a national level, we could only link patient level data to positive microbiology using the *Electronic Communication of Surveillance in Scotland* registry. As such, it was neither possible to determine what proportion of the remaining 1,317 cases were associated with sterile blood cultures, nor what

proportion had no blood cultures performed. However, extrapolating from our validation data, where 87.5% of all cases had blood cultures performed, we assume that the vast majority of the 1,317 cases also had blood cultures performed with a significant proportion yielding no growth.

Staphylococcus (403/950, 42.4%), streptococcus (337/950, 35.5%) and enterococcus (85/950, 8.9%) were the most common organisms identified ***(Supplementary figure 5)***. The majority of staphylococci were *Staphylococcus aureus* (301/403, 74.7%,). Across the years, positive microbiology rate increased from 34.7% in 2008 to 45.4% in 2014 ***(Supplementary figure 6)***. Several factors were associated with 30 day and 1 year mortality ***(Supplementary figure 7*** *and* ***Figure 3****, respectively)*. Compared to patients without positive blood cultures, those with *Staphylococcus aureus* and enterococcus were at the highest risk of 1 year mortality (OR 4.34 [95% CI 3.12-6.05] and 3.41 [95% CI 2.04-5.70], respectively).

In our sensitivity analysis restricting the cohort to the first diagnostic code position, positive blood cultures were identified in 63% (753/1,195) of patients ***(Supplementary figure 8)***. Similar to the primary analysis, those with *Staphylococcus aureus* and enterococcus were at the highest risk of 1 year mortality (OR 2.23 [95% CI 1.47 - 3.39] and 1.89 [95% CI 1.05 – 3.42] respectively), compared to patients without positive blood cultures ***(Supplementary figure 9)***.

Discussion

In this nationwide population cohort study using individual patient-level data linkage, we make several important observations. First, while the estimated overall crude incidence of infective endocarditis has remained relatively stable from 1995 onwards. When stratified by age, there was a two-fold increase in incidence in the elderly but either decreasing or static rates in younger patients. Second, the adjusted case fatality rate following endocarditis remains high but has declined over the last 25 years. Following adjustment for age and comorbidity, men had overall higher case fatality rates than women. Third, less than half of all patients had positive blood cultures, with the overall positive blood culture rate increasing from 35% in 2008 to just under half in 2014. Where a causative organism was identified, staphylococcus and streptococcus were the most common species. Fourth, compared to patients no positive blood cultures, patients with *Staphylococcus aureus* or enterococcus bacteremia had the highest risk of death. Finally, and perhaps of most clinical relevance, our analysis has shown that the 2008 change in antibiotic prophylaxis guidelines in the United Kingdom has not resulted in a significant rise in incident cases of infective endocarditis.

Population-based studies in endocarditis remain scarce with the majority of epidemiology extrapolated from hospital-based cohorts or cross-sectional studies.[19, 20] Our dataset included cases of infective endocarditis over the last 25 years. Whilst we only had positive blood culture data for a fifth of this period, evaluating the overall period allowed us to investigate long-term trends in incidence of and outcomes following infective endocarditis. With the exception of recent large population-based time-series analyses evaluating the temporal incidence of endocarditis in England[4,21] and United States,[7, 22] the majority of studies are limited by sample size, consisting of fewer than one thousand patients.[20] All of these studies are further limited by incomplete characterization of participant demographics and characteristics, including

comorbidity, case-fatality rates and microbiology. Using an established national linkage approach in Scotland,[23, 24] we identified over 7,000 hospitalizations with a diagnosis of infective endocarditis and provide detailed individual patient-level information on baseline demographics, comorbidity burden, associated microbiology data and subsequent case fatality rates.

As such, there are several strengths to our study. First, our approach ensured complete follow-up in those patients who remained resident in Scotland during the study period. Indeed, similar linkages have already been used to deliver randomized clinical trials[23, 25] and cohort studies[24] in Scotland. Second, our cohort consisted of consecutive patients hospitalized with a diagnostic code for infective endocarditis, avoiding selection bias and ensuring that our study population was representative. Third, unlike previous administrative data assets utilising diagnostic coding data to determine culture status,[7, 22] which may not have been restricted to blood stream infections, we have used primary patient-level data from Scottish microbiology laboratories to ensure accurate recording of positive blood culture status. Fourth, using source clinical data, we validated the accuracy of the diagnostic coding including code position and microbiology data using data from local microbiology laboratory information systems (ensuring consistency with the national microbiology surveillance systems across Scotland).

Three relatively recent guideline updates have emerged from the National Institute of Health and Care Excellence[18] in the United Kingdom, the American Heart Association (AHA)[26] and the European Society of Cardiology.[2] These guidelines have recommended either complete or partial cessation of antibiotic prophylaxis in patients at moderate or high risk of infective endocarditis. Subsequent analyses evaluating the incidence of infective endocarditis have shown contrasting results. In England, a significant reduction in antibiotic prescriptions and an

apparent rise in the incidence of endocarditis was observed following the introduction of changes to NICE guidelines.[2,4] Similar results were noted in a US-based population comparing incidence before and after changes to antibiotic prophylaxis guidelines in 2007.[7] In contrast, three studies from the United States showed no increase in incidence following changes to antibiotic prophylaxis guidelines.[8,27,28] These studies, however, were either limited in terms of cohort size[8] or evaluated incidence over a shorter time frame following the change in guidelines.[27] Furthermore, small but well-characterized populations in the United States[29] and France[10] have also reported static incident rates. In our study, the crude incident rate of infective endocarditis increased in Scotland from 1990 until 1995 but remained relatively static thereafter, suggesting that changes to clinical guidelines regarding antibiotic prophylaxis were not associated with an adverse effect on the incidence of infective endocarditis in Scotland.

We observed an important interaction between age and rates of endocarditis. The incidence in patients over the age of 80 increased two-fold, whilst remaining static or decreasing in younger populations. This striking increase in the elderly is multifactorial and most likely reflects changes in the incidence of degenerative valvular heart disease, a rise in the number of patients surviving with multiple comorbidities, an increase in the provision of invasive therapeutic interventions including implantable cardiac devices (pacemakers, defibrillators, closure devices and percutaneous valve technology)[30] and hemodialysis,[31] and more extensive investigations[32] in frail, elderly patients.

We report important differences in the microbiology of patients with infective endocarditis compared to many studies in the existing literature. In our study, with linkage to a robust national microbiology laboratory blood culture dataset, no causative organism was identified in the majority (57%) of patients. In the published literature, culture-negative endocarditis

varied from 15% to 60% across both hospital-based cohorts[20, 33] and population registries based primarily on US populations.[7, 22, 34] Several reasons might explain our low culture positive rates. First, we defined infective endocarditis using diagnostic coding. Whilst this is more sensitive and eliminated selection bias, it is possible that the lower rates of culture positive cases reflect lower specificity by including some patients with lower probability of infective endocarditis. We validated the accuracy of the diagnostic coding using an in-depth health record review of nearly 400 cases. Restricting the patient population to the first two diagnostic positions gave an overall positive predictive value for definite or probable diagnosis of infective endocarditis of 88%. As such, case ascertainment bias due to coding error is unlikely to have made a significant contribution. Second, from 2009 to 2012, three laboratories did not provide complete microbiology data for national linkage. These laboratories were small and served <1.5% of the Scottish population and would therefore have a negligible effect on the rates of positive blood cultures. Third, across most hospitalized cohorts of patients with infective endocarditis, cases were identified by the attending clinician.[35] A high culture positive rate in these cohorts may therefore reflect selection bias towards patients with positive blood cultures.[11] Across population registry data, the culture-negative rates were higher[7, 22] with similar rates to those observed in Scotland.[34] Fifth, across both population registries[7, 22] and some hospital-based cohorts,[36] culture status was not restricted to blood cultures but also included tissue cultures including valves and serological tests, invariably increasing the rates of culture positive diagnosis.[36] Reassuringly, where positive blood cultures were obtained in our cohort, streptococcus and staphylococcus were the most commonly identified pathogens, consistent with the wider literature.[37, 38] Finally, we noticed a relative rise of 16% in the proportion of patients with culture positive infective endocarditis from 2008 to 2014. This observation likely reflects more judicious timing of administration of antibiotic treatment and

ensuring blood cultures are taken prior to initiation of therapy; clinical practice that has been emphasized in recent international guidelines.[39]

Across the study cohort, crude temporal mortality rates at one year remained stable, ranging from 27% to 33%. However, after adjustment, we observed a steady reduction in mortality. A recent large US based study showed a similar relationship with decreasing mortality over a similar time period[22] whilst others have shown little or no change in case fatality.[4, 40] Positive microbiology was independently associated with poorer outcomes. *Staphylococcus aureus* bacteremia was independently associated with a four-fold increased mortality rate at 30 days and one year. In contrast, the magnitude of association for enterococcus bacteremia changed from a two-fold increased risk at 30 days to three-fold increased risk at one year. This observation likely reflects a frailer and older population that is more susceptible to enterococcus bacteremia[41, 42] and at higher risk of medium- to long-term mortality.[43-45]

Limitations

There are several limitations to our study. First, index cases and comorbidity were defined using administrative datasets, which are subject to inaccurate coding. However, we improved coding specificity for infective endocarditis using data from our validation work. To ensure a reasonable balance between specificity and sensitivity, we included all hospitalizations with a diagnostic code appearing in the first two (of six) positions only. Restricting the population to the first diagnostic position markedly reduced the sensitivity for infective endocarditis in previous literature.[22] Second, for our validation exercise, the diagnosis of infective endocarditis was based on a clinician documented diagnosis of infective endocarditis. Whilst we acknowledge that the Modified Duke Criteria represent the 'gold standard' for defining cases of infective endocarditis,[2] unfortunately the vast majority of clinicians did not reference these

criteria in clinical notes entered on electronic patient records. For example, the presence or absence of physical exam findings relevant to the minor criteria (e.g. vascular or immunologic phenomena) were frequently not documented. After careful consideration of the impact of these missing data and the potential for introducing significant bias, our research team elected to employ a more pragmatic approach with 'true' cases of infective endocarditis defined as those clinically documented and treated as infected endocarditis. Third, we could not differentiate patients with blood culture negative infective endocarditis from those patients in whom blood cultures were not performed. From our validation work, we suspect that just over 10% of all patients will fall into the latter category. Fourth, whilst we have attempted to address the majority of confounders, residual unmeasured confounding may have affected the trends observed in case fatality rates and the associations evaluating microbiology and risk of mortality.

Conclusion

We report important temporal changes in patients with infective endocarditis in the Scottish population over the past 25 years. The crude incidence of infective endocarditis increased from 1990 to 1995 but has remained relatively static thereafter. Importantly, the incidence has increased two-fold in the elderly. Both short- and long-term adjusted case fatality rates of infective endocarditis have shown a steady decrease over the last 25 years. Finally, and most interestingly, the majority of patients with infective endocarditis in our cohort did not have positive blood cultures. In those patients with positive microbiology, staphylococcus and enterococcus conferred the highest risk of all-cause mortality. Our data highlight that infective endocarditis remains a lethal condition, especially in the elderly. We also demonstrate the importance of microbiology data for prognostication, not only for in-hospital mortality, but also for medium-term outcomes. As such, our data further support the multi-disciplinary

integration of cardiology, microbiology and infectious disease teams as advocated by international guidelines to optimize diagnosis and patient care.[2]

Acknowledgements and funding

This study was funded by the British Heart Foundation through an Intermediate Clinical Research Fellowship (FS/19/17/34172), Clinical Research Training Fellowship (FS/18/25/33454), Senior Clinical Research Fellowship (FS/16/14/32023) and a Research Excellence Award (RE/18/5/34216). DAM is supported by a Wellcome Trust Intermediate Clinical Fellowship (201492/Z/16/Z). DEN is supported by the British Heart Foundation (CH/09/002, RG/16/10/32375, RE/18/5/34216) and a Wellcome Trust Senior Investigator Award (WT103782AIA).

Disclosures

None

Figures and tables

Figure 1: Estimated incidence rate per 100,000 in the population (A) and stratified by age groups (B).

Blue circles in A represent the absolute crude rates with the size of the circles proportional to the absolute count. The solid blue line represents the estimated incident rate from generalized additive modelling using the Poisson distribution. The dashed blue lines represent the corresponding upper and lower 95% confidence interval bounds.

Figure 2: Plot showing the observed incident rates per 100,000 by year of hospitalization (black dots), in relation to the introduction of national antibiotic prophylaxis guidelines.

The shaded grey box indicates introduction of NICE antibiotic prophylaxis guidelines. The black line shows the predicted incident rate using the model described in Supplementary text 6, incorporating the change in guidelines from 2008 onwards. The overlying red line shows the predicted incident rate assuming the counterfactual of no change in antibiotic prophylaxis guidelines in 2008.

Figure 3: Forest plot showing odds ratio from logistic regression evaluating the association between all-cause mortality at 1 year and patient demographics, comorbidity and microbiology.

Table 1: Baseline characteristics and outcomes in patients hospitalized with infective endocarditis, stratified by 5 year calendar groups.

Table 2: Baseline characteristics and outcomes in patients hospitalized with infective endocarditis, stratified by blood culture status and organism identified.

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Table 1

	Calendar years in 5 year groups				
	1990 - 1994	**1995 - 1999**	**2000 - 2004**	**2005 - 2009**	**2010 - 2014**
Number of patients, n	**1379**	**1642**	**1464**	**1537**	**1616**
Baseline characteristics					
Age, years (SD)	62.10 (17.25)	64.62 (16.34)	65.32 (17.59)	66.01 (16.92)	66.56 (17.96)
Women, n (%)	771 (55.9)	855 (52.1)	775 (52.9)	751 (48.9)	768 (47.5)
Deprivation index, n (%)					
Rank 1 (most deprived)	402 (29.4)	404 (24.7)	387 (26.6)	369 (24.1)	365 (22.7)
Rank 2	327 (23.9)	363 (22.2)	351 (24.1)	326 (21.3)	376 (23.4)
Rank 3	233 (17.1)	310 (19.0)	257 (17.7)	318 (20.7)	319 (19.9)
Rank 4	223 (16.3)	276 (16.9)	254 (17.5)	273 (17.8)	274 (17.1)
Rank 5 (least deprived)	181 (13.3)	282 (17.2)	205 (14.1)	248 (16.2)	271 (16.9)
Previous medical conditions/interventions					
Myocardial infarction, n (%)	59 (4.3)	89 (5.4)	60 (4.1)	65 (4.2)	80 (5.0)
Cerebrovascular disease, n (%)	68 (4.9)	108 (6.6)	83 (5.7)	82 (5.3)	75 (4.6)
Heart failure hospitalization, n (%)	220 (16.0)	315 (19.2)	251 (17.1)	206 (13.4)	173 (10.7)
Cardiac device, n (%)	25 (1.8)	45 (2.7)	48 (3.3)	42 (2.7)	48 (3.0)
Prior cardiac valvular surgery, n (%)	151 (10.9)	161 (9.8)	136 (9.3)	119 (7.7)	130 (8.0)
Outcomes at 30 days					
All-cause death, n (%)	196 (14.2)	233 (14.2)	231 (15.8)	198 (12.9)	223 (13.8)
Heart failure hospitalization, n (%)	41 (3.0)	58 (3.5)	75 (5.1)	84 (5.5)	74 (4.6)
Subsequent valve surgery, n (%)	64 (4.6)	77 (4.7)	66 (4.5)	73 (4.7)	86 (5.3)
Outcomes at 1 year					
All-cause death, n (%)	435 (31.5)	515 (31.4)	490 (33.5)	486 (31.6)	500 (30.9)
Heart failure hospitalization, n (%)	189 (13.7)	215 (13.1)	177 (12.1)	191 (12.4)	158 (9.8)
Subsequent valve surgery, n (%)	141 (10.2)	155 (9.4)	157 (10.7)	179 (11.6)	181 (11.2)

Table 2

	Culture negative/ no cultures	Staphylococcus aureus	Staphylococcus (Coagulase negative)	Streptococcus	Enterococcus	Polymicrobial / other
Number of patients, n	1317	301	102	337	85	125
Age, years	69.5 (16.9)	58.92 (19.09)	65.41 (14.95)	63.35 (17.39)	70.28 (13.06)	60.83 (19.22)
Women, n (%)	735 (55.8)	113 (37.5)	40 (39.2)	107 (31.8)	29 (34.1)	53 (42.4)
Deprivation index, n (%)						
Rank 1 (most deprived)	279 (21.3)	92 (30.7)	21 (20.6)	73 (21.7)	29 (34.1)	33 (26.6)
Rank 2	320 (24.5)	69 (23.0)	23 (22.5)	47 (14.0)	21 (24.7)	40 (32.3)
Rank 3	286 (21.9)	54 (18.0)	17 (16.7)	70 (20.8)	13 (15.3)	17 (13.7)
Rank 4	218 (16.7)	44 (14.7)	23 (22.5)	70 (20.8)	11 (12.9)	20 (16.1)
Rank 5 (least deprived)	205 (15.7)	41 (13.7)	18 (17.6)	76 (22.6)	11 (12.9)	14 (11.3)
Previous medical conditions/interventions						
Myocardial infarction, n (%)	68 (5.2)	12 (4.0)	8 (7.8)	17 (5.0)	< 5	5 (4.0)
Cerebrovascular disease, n (%)	62 (4.7)	13 (4.3)	7 (6.9)	15 (4.5)	9 (10.6)	6 (4.8)
Heart failure hospitalization, n (%)	157 (11.9)	29 (9.6)	14 (13.7)	34 (10.1)	6 (7.1)	18 (14.4)
Cardiac device, n (%)	27 (2.1)	12 (4.0)	8 (7.8)	< 5	< 5	6 (4.8)
Cardiac valve surgery, n (%)	71 (5.4)	17 (5.6)	27 (26.5)	30 (8.9)	10 (11.8)	16 (12.8)
Chronic respiratory disease, n (%)*	195 (19.1)	36 (14.8)	13 (15.5)	58 (20.7)	16 (22.5)	16 (16.2)
Diabetes mellitus, n (%)*	133 (13.0)	35 (14.4)	22 (26.2)	30 (10.7)	11 (15.5)	18 (18.2)
Outcomes at 30 days						
All-cause death, n (%)	130 (9.9)	130 (9.9)	71 (23.6)	26 (25.5)	49 (14.5)	12 (14.1)
Heart failure hospitalization, n (%)	78 (6.0)	6 (2.0)	< 5	15 (4.5)	< 5	7 (5.6)
Subsequent valve surgery, n (%)	23 (1.8)	35 (11.6)	5 (4.9)	46 (13.6)	5 (5.9)	7 (5.6)
Outcomes at 1 year						
All-cause death, n (%)	336 (25.5)	133 (44.2)	46 (45.1)	99 (29.4)	43 (50.6)	41 (32.8)
Heart failure hospitalization, n (%)	159 (12.1)	18 (6.0)	10 (9.8)	33 (9.8)	6 (7.1)	16 (12.8)
Subsequent valve surgery, n (%)	87 (6.6)	54 (17.9)	18 (17.6)	85 (25.2)	9 (10.6)	19 (15.2)

** Based on community prescribing (see Supplementary text 5)*

Figure 1

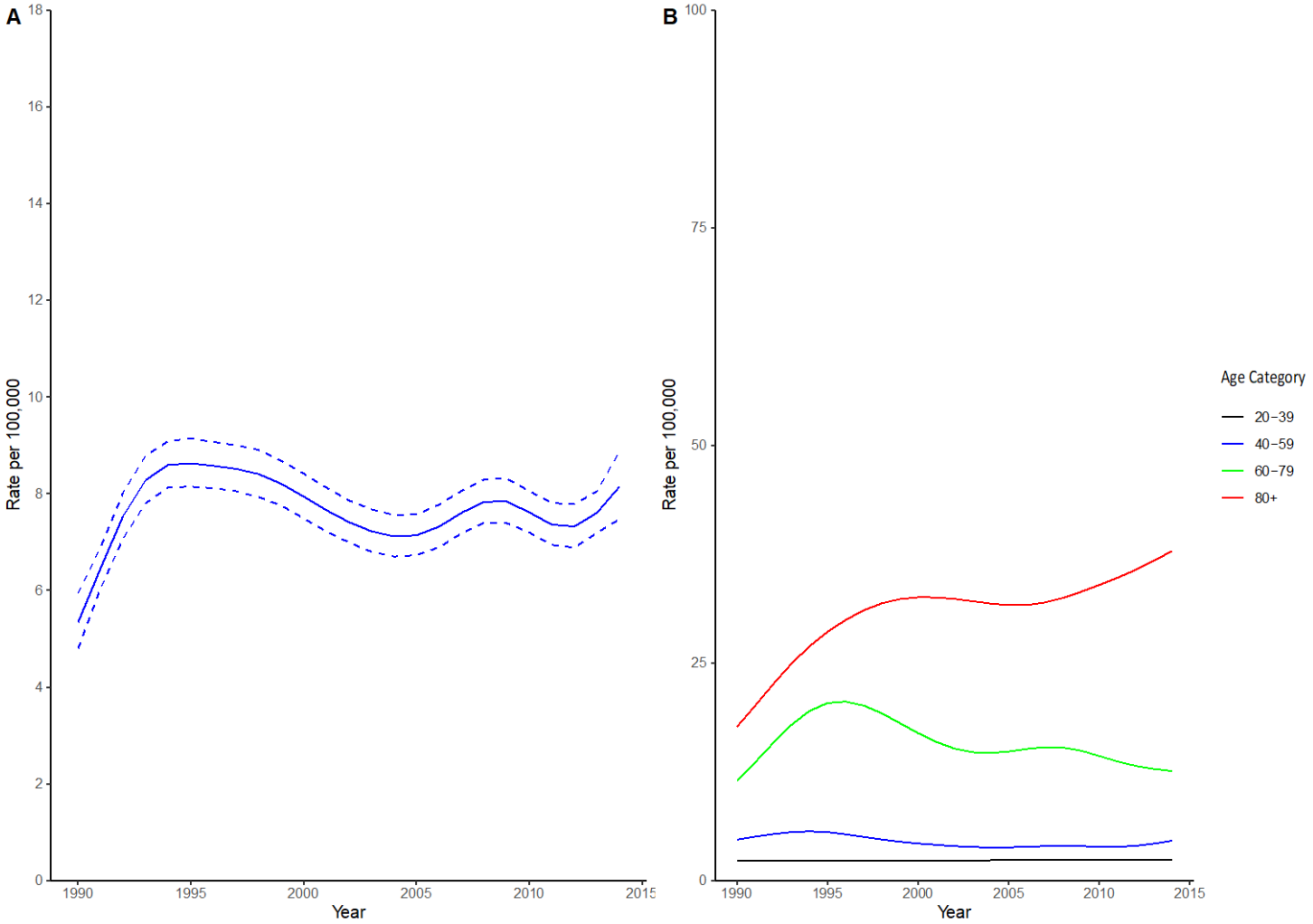

A
Rate per 100,000
Year
B
Rate per 100,000
Year
Age Category
20–39
40–59
60–79
80+

Figure 2

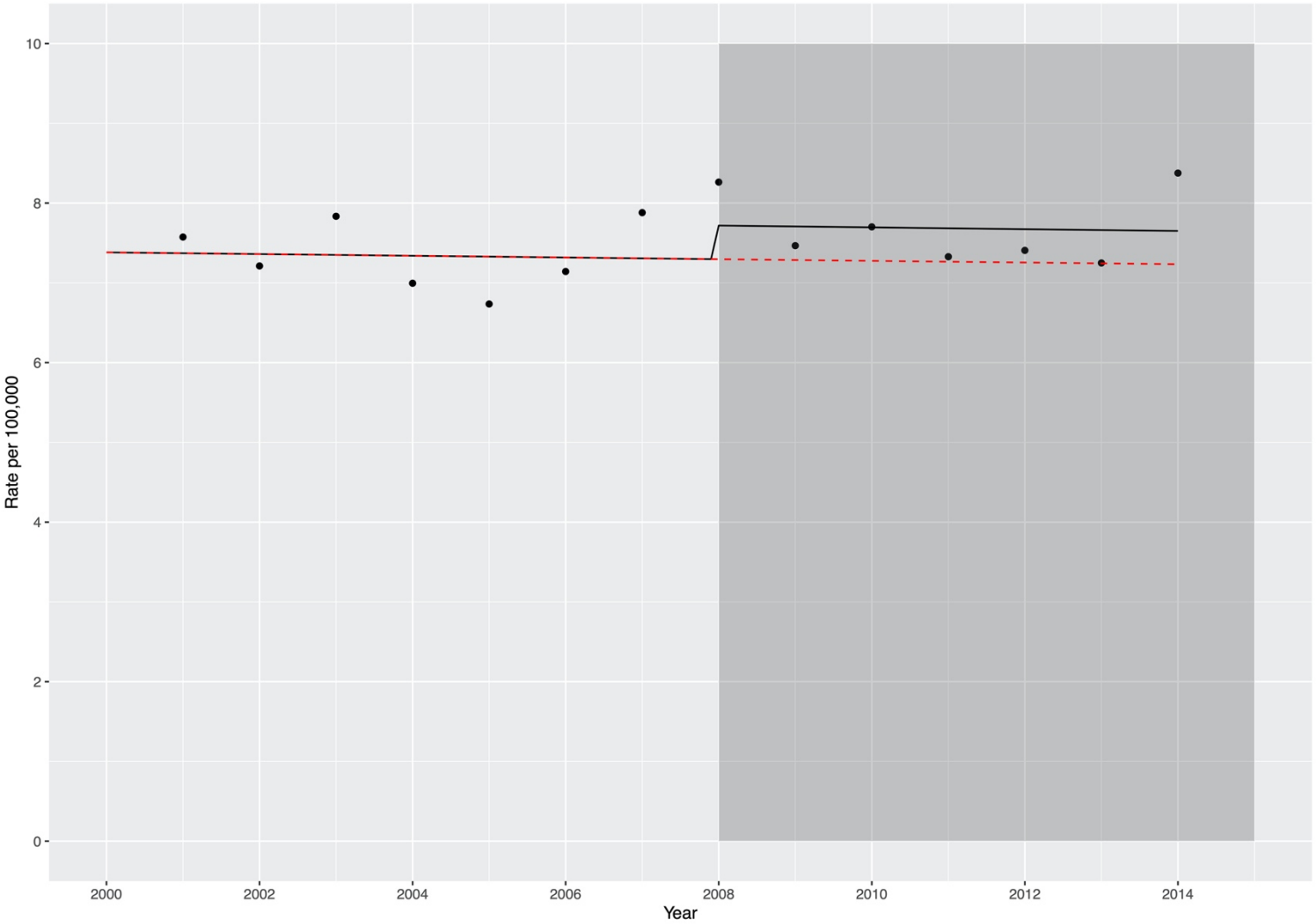
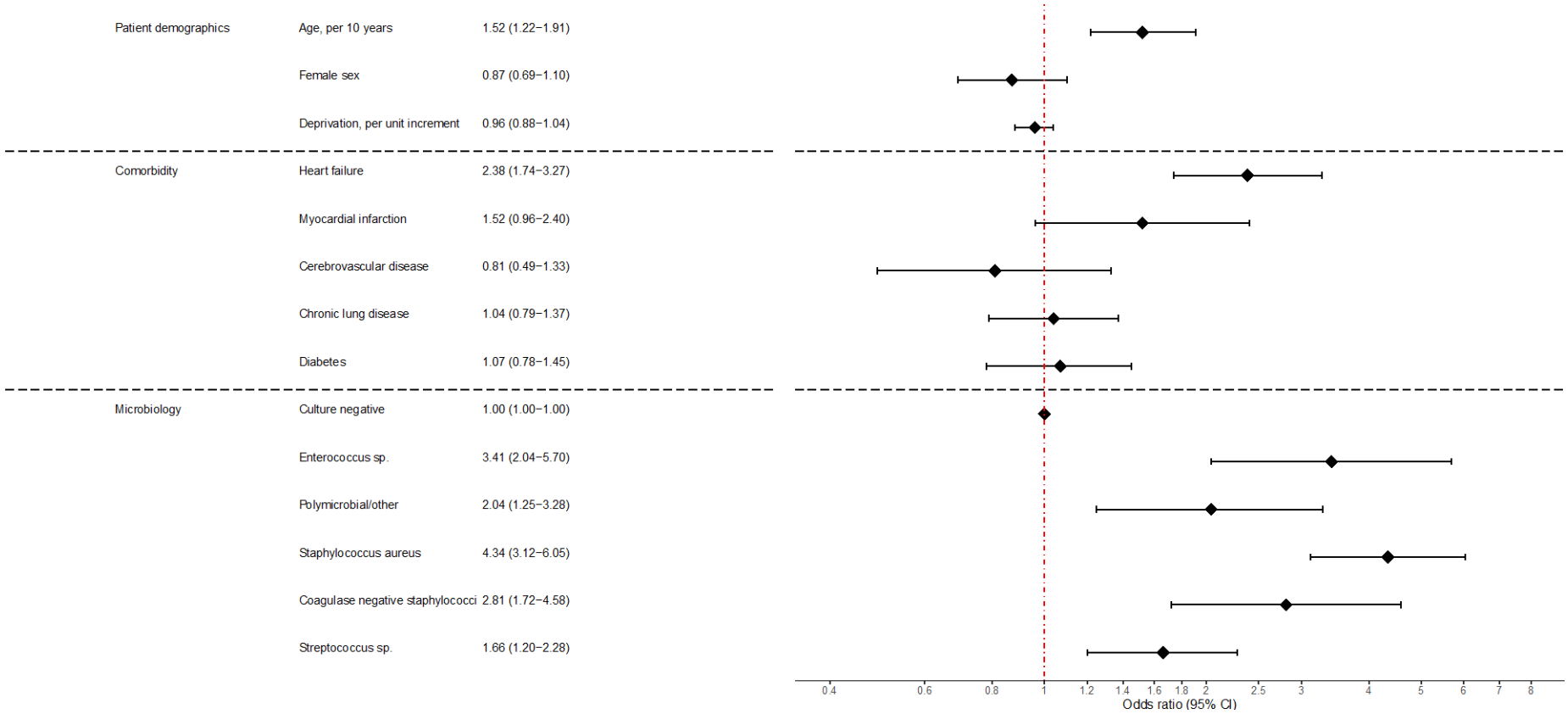

10
8
6
4
2
0
Rate per 100,000
2000
2002
2004
2006
2008
2010
2012
2014
Year

Figure 3


Patient demographics
Age, per 10 years
1.52 (1.22−1.91)
Female sex
0.87 (0.69−1.10)
Deprivation, per unit increment
0.96 (0.88−1.04)
Comorbidity
Heart failure
2.38 (1.74−3.27)
Myocardial infarction
1.52 (0.96−2.40)
Cerebrovascular disease
0.81 (0.49−1.33)
Chronic lung disease
1.04 (0.79−1.37)
Diabetes
1.07 (0.78−1.45)
Microbiology
Culture negative
1.00 (1.00−1.00)
Enterococcus sp.
3.41 (2.04−5.70)
Polymicrobial/other
2.04 (1.25−3.28)
Staphylococcus aureus
4.34 (3.12−6.05)
Coagulase negative staphylococci
2.81 (1.72−4.58)
Streptococcus sp.
1.66 (1.20−2.28)
0.4
0.6
0.8
1
1.2
1.4
1.6
1.8
2
2.5
3
4
5
6
7
8
Odds ratio (95% CI)

ONLINE SUPPLEMENT

Incidence, microbiology and outcomes in patient hospitalized with infective endocarditis

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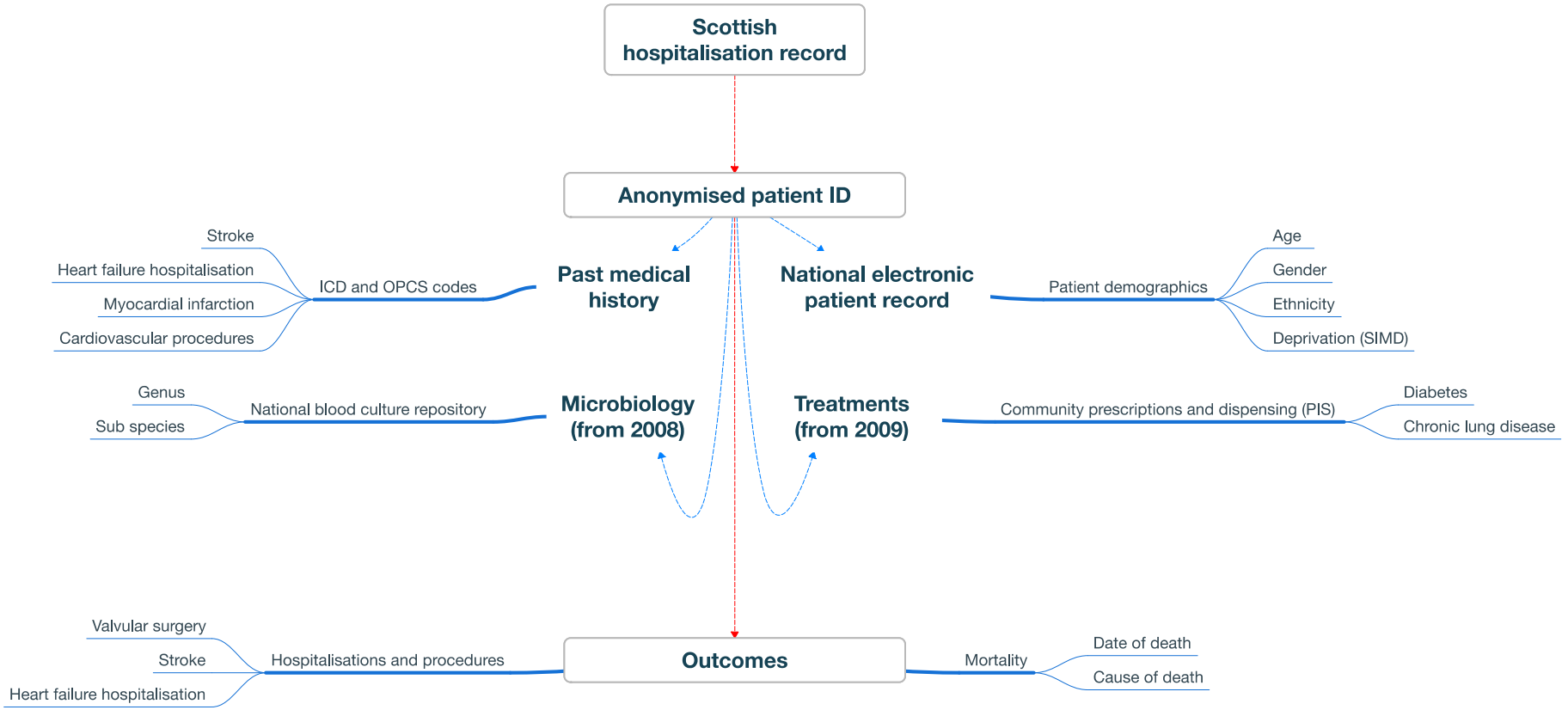
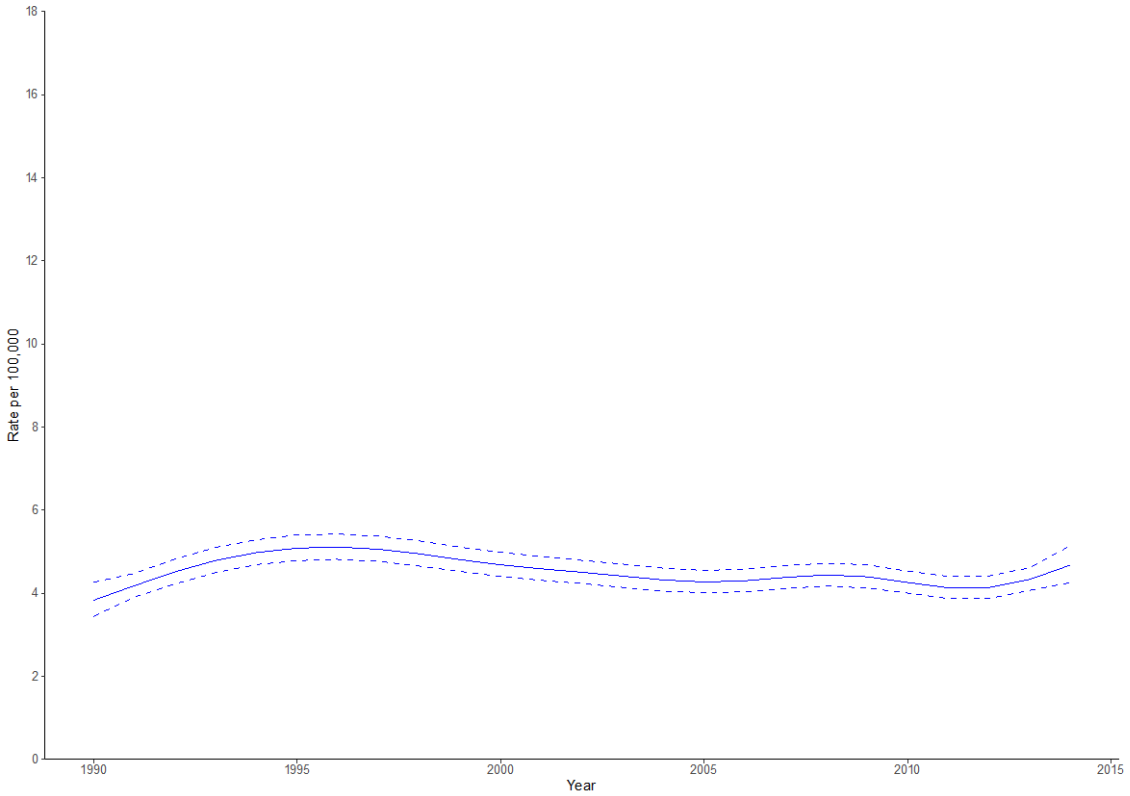
Supplementary figures

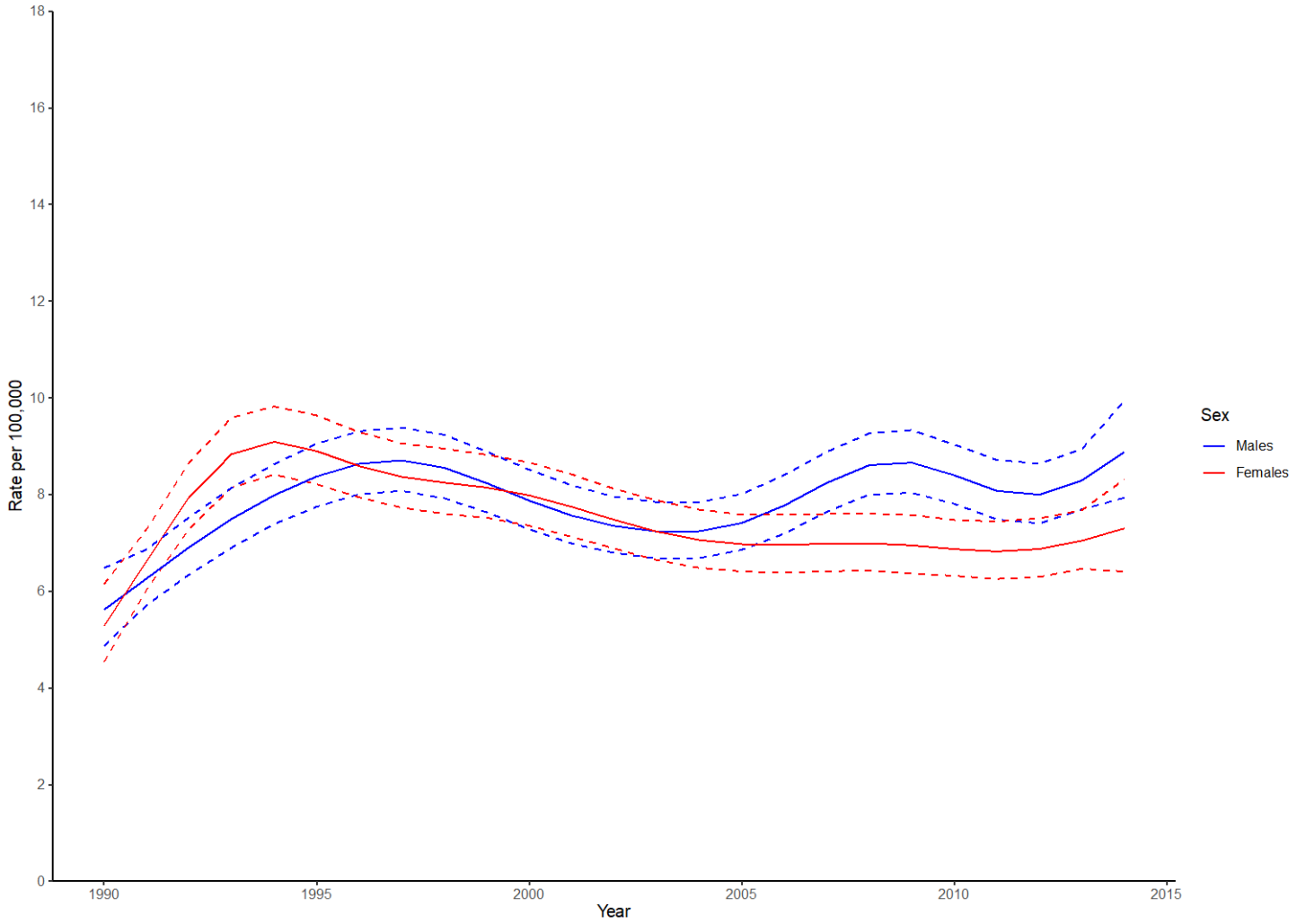
Supplementary figure 1*: *Map summarising linkage of national data assets to define the study population and subsequent longitudinal follow up. Nomenclature: Anonymised patient ID- Community Health Index (CHI) number; Community prescriptions and dispensing- Prescribing Information System (PIS); National blood culture repository- Electronic communication of surveillance in Scotland (ECOSS); Scottish hospitalization record- Scottish Morbidity Record (SMR) 01.



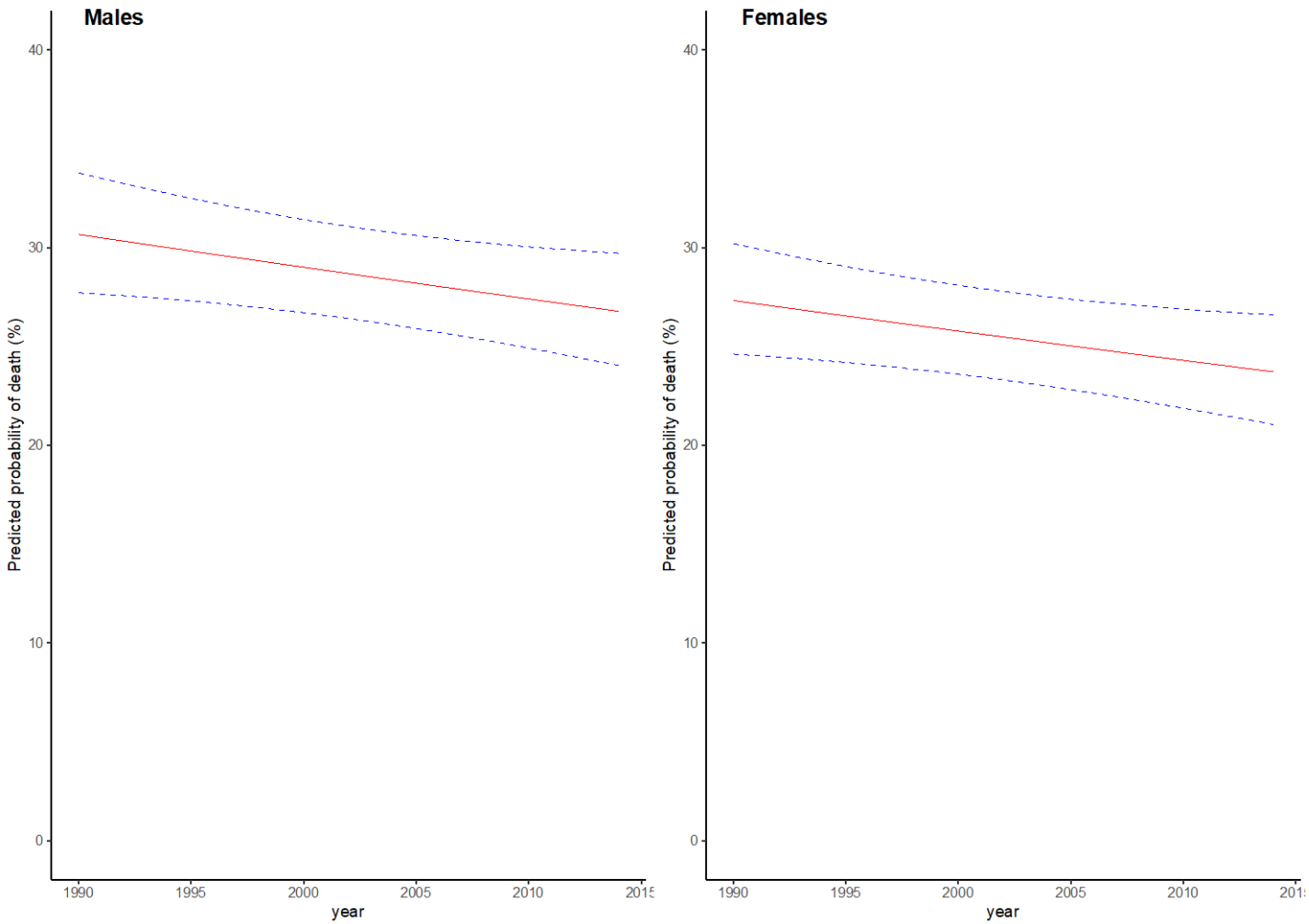
Supplementary figure 2: Sensitivity analysis restricting to diagnostic coding in position one (primary diagnosis). Estimated incidence rate per 100,000 in the population. Blue circles represent the absolute crude rates with the size of the circles proportional to the absolute count.



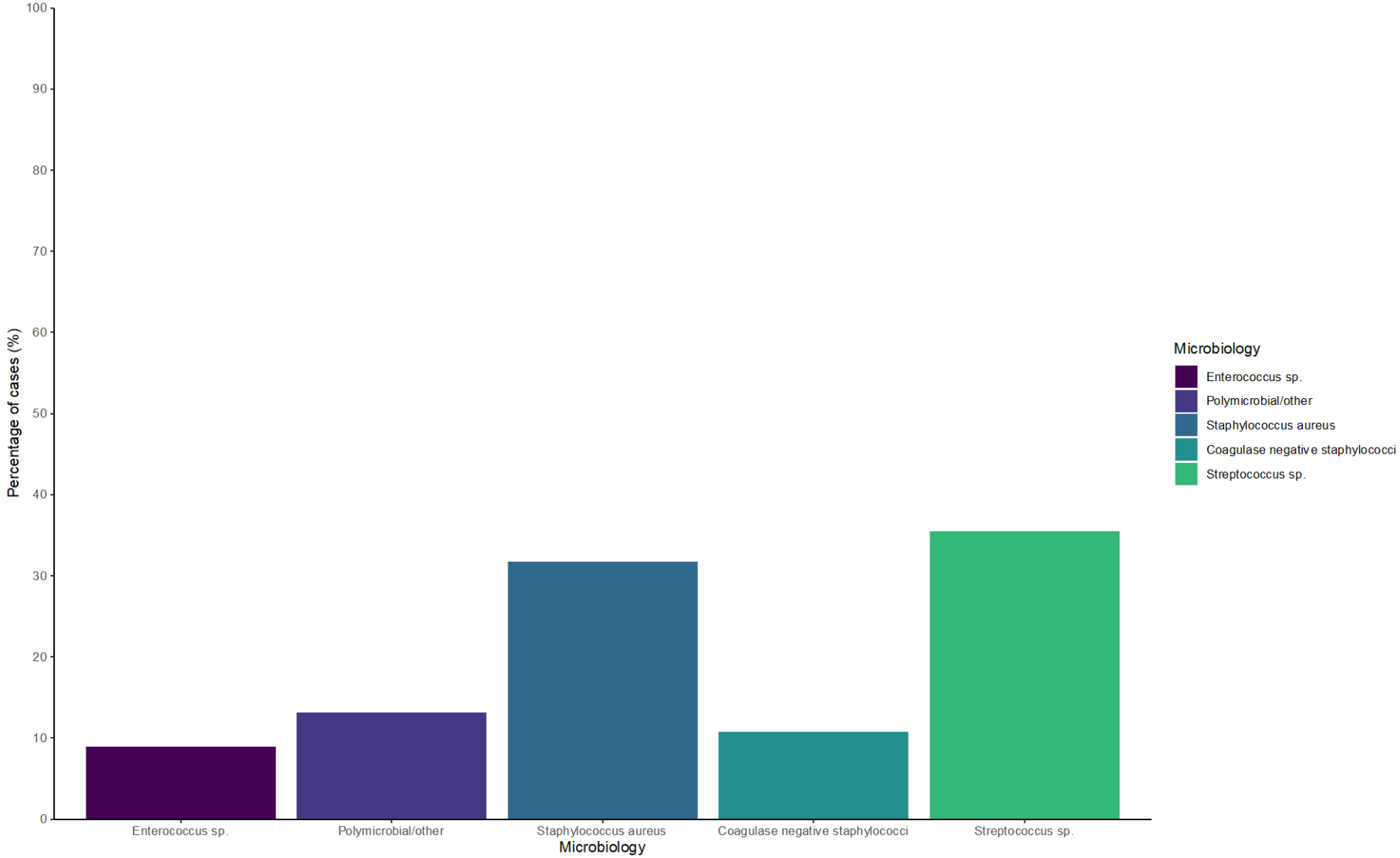
Supplementary figure 3: Estimated incidence rate per 100,000 stratified by sex.



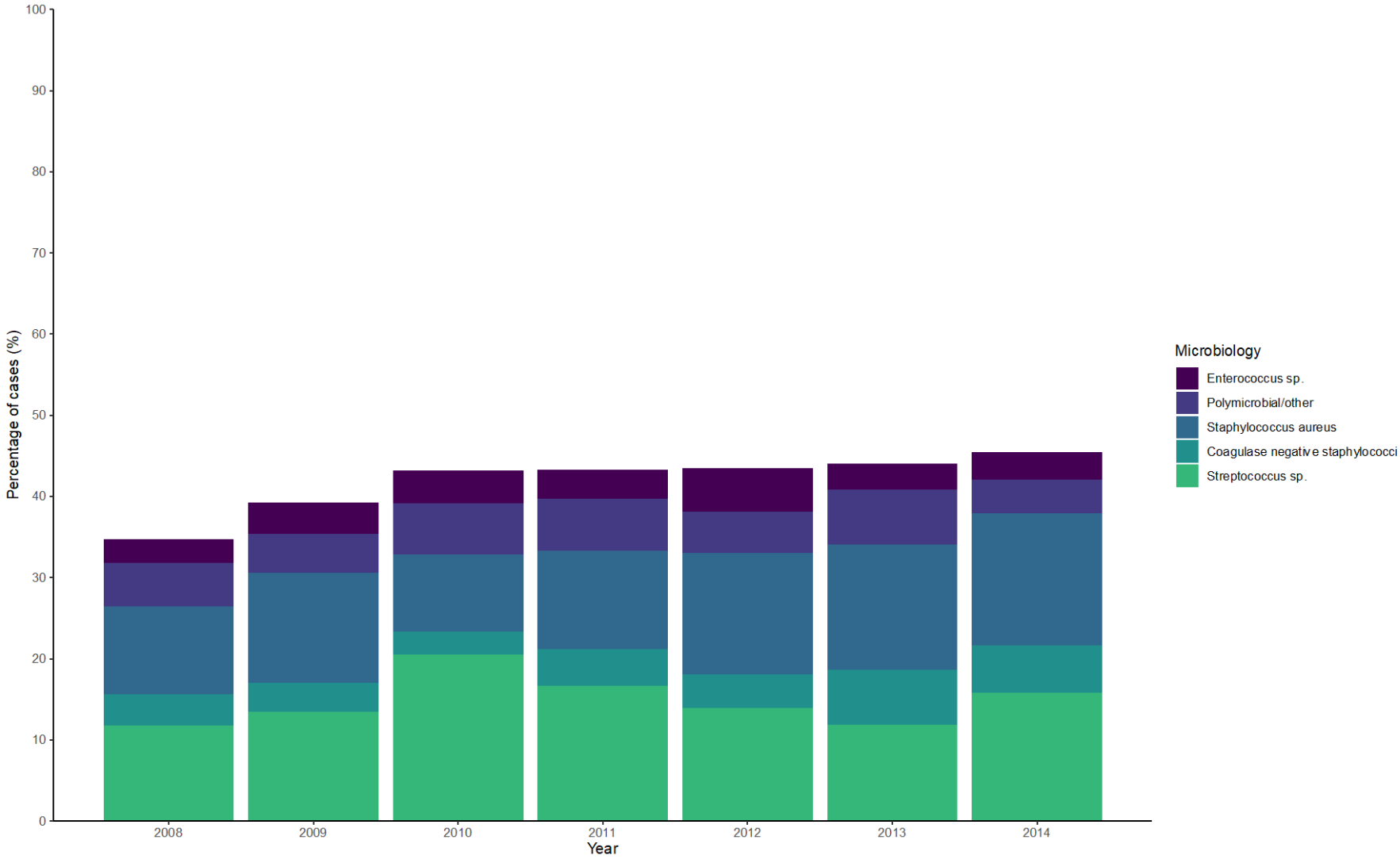
Supplementary figure 4: Predicted one-year mortality following incident endocarditis in men and women.



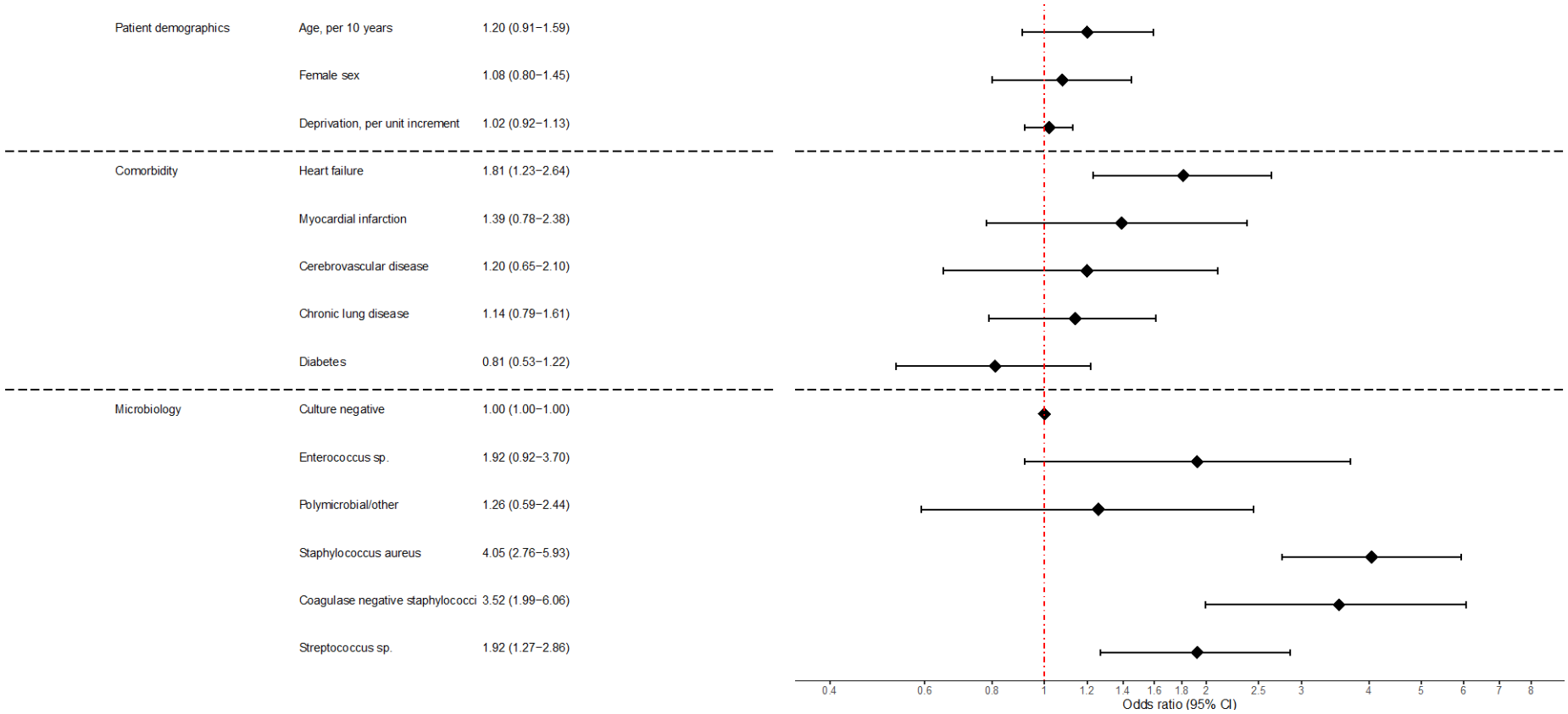
Supplementary figure 5: Positive blood culture microbiology stratified by species



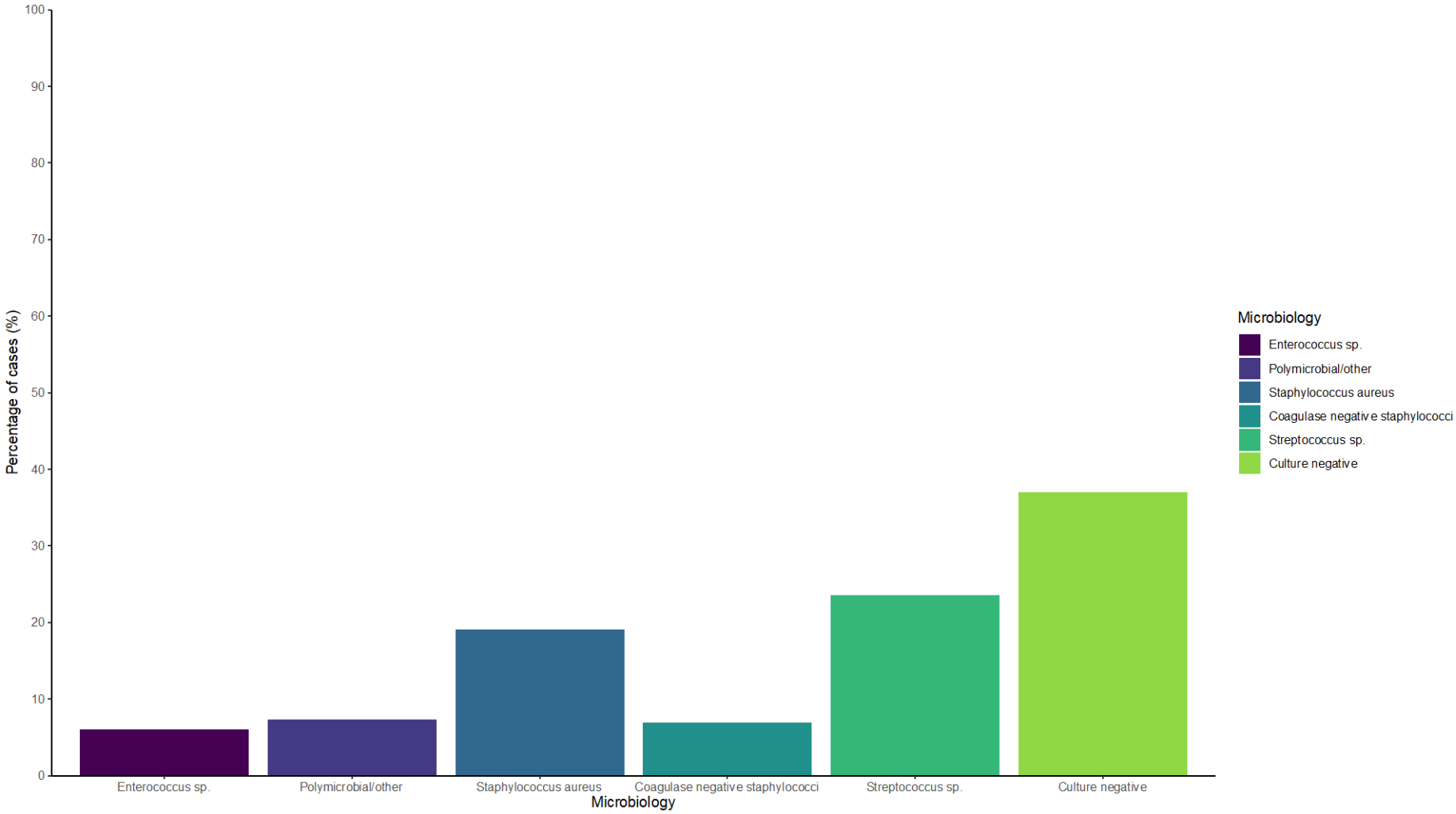
Supplementary figure 6: Stack plot showing microbiology by year



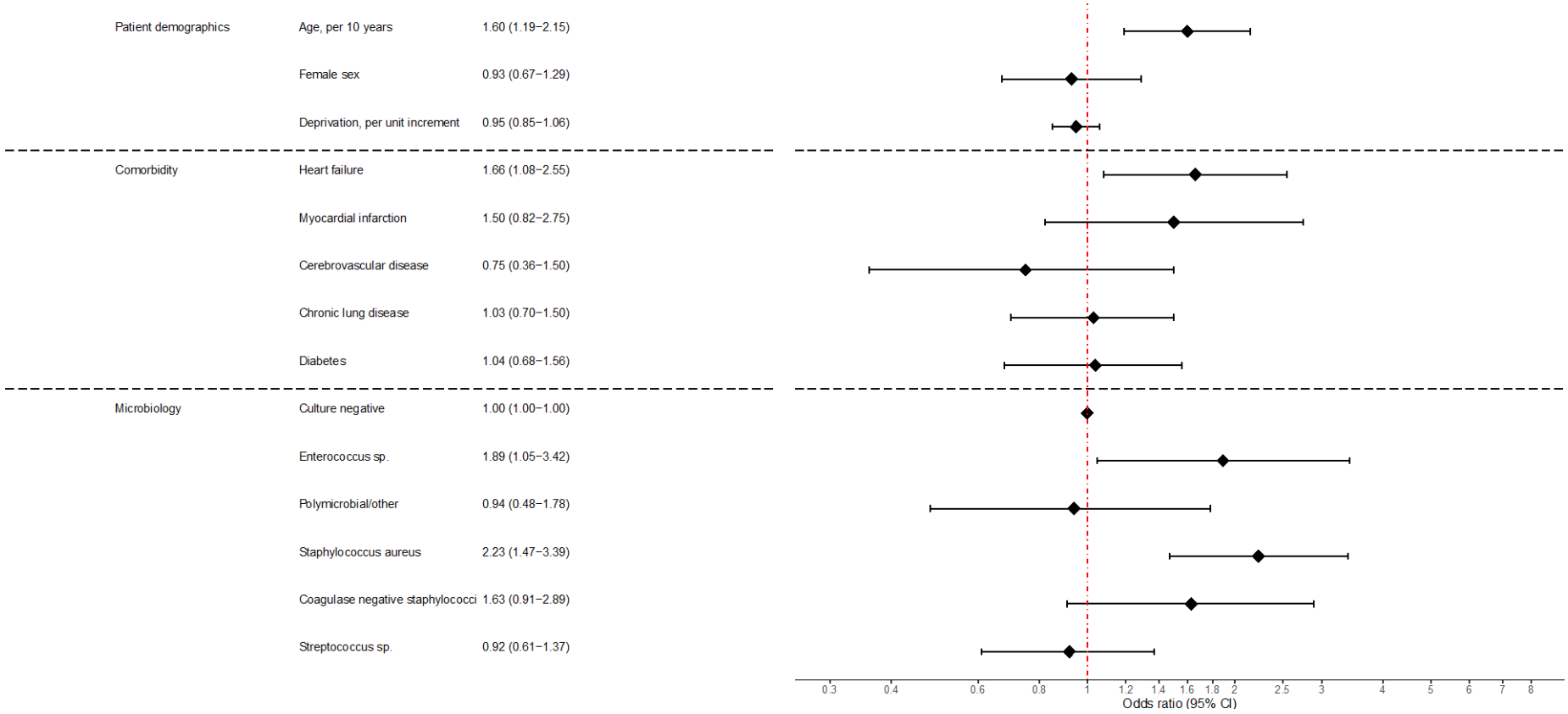
Supplementary figure 7: Forest plot showing association of microbiology and risk of mortality at 30 days



Supplementary figure 8: Sensitivity analysis restricting diagnostic coding to position one. Microbiology status and organism identified.



Supplementary figure 9: Sensitivity analysis restricting to diagnostic coding in position one. Forest plot showing association of microbiology and risk of mortality at 1 year



Supplementary text

Supplementary text 1: Descriptions and sources of national data assets used for individual patient level linkage

Scottish hospitalization record

Scottish hospitalizations from infective endocarditis were defined from the Scottish morbidity record 01 (SMR01) - General/Acute Inpatient & Day Case. SMR01 is an episode-based patient record relating to all inpatients and day cases discharged from non-obstetric and non-psychiatric specialties. A record is generated when a patient completes an episode of inpatient or day case care. Data collected include patient identifiable and demographic details, episode management details and general clinical information. Currently diagnoses are recorded using the ICD-10 classification and operations are recorded using the OPCS-4 classification. Further information on the national dataset and variables contained is available at https://www.ndc.scot.nhs.uk/Data-Dictionary/SMR-Datasets//Episode-Management/SMR-Record-Type/

Past history, operation codes and demographics were also derived from the Scottish Morbidity Record 01 and linked to incident cases of infective endocarditis. Subsequent hospitalizations based on ICD codes are further linked to incident cases of infective endocarditis identified.

National Records of Scotland (NRS)

The NRS covers all deaths in Scotland with approximately 55,000 deaths registered annually. The National Records of Scotland Death Records are linked with the NHS Scotland Scottish Morbidity Database which links together NHS Scotland inpatient, mental health and cancer registry datasets with the NRS Death Records.

Death status, cause of death and date of death were linked to the patients defined as having incident infective endocarditis.

Further information of the NRS death registry is available at https://www.ndc.scot.nhs.uk/National-Datasets/data.asp?SubID=13

Prescribing Information System (PIS)

The Prescribing Information System (PIS) is the definitive data source for all prescribing relating to all medicines and their costs that are prescribed and dispensed in the community in Scotland. The information is supplied by Practitioner & Counter Fraud Services Division (P&CFS) who is responsible for the processing and pricing of all prescriptions dispensed in Scotland. Primary care physicians write the vast majority of these prescriptions, with the remainder written by other authorised prescribers such as nurses and dentists. Also included in the dataset are prescriptions written in hospitals that are dispensed in the community. Note that prescriptions dispensed within hospitals are not included.

Both the diabetes and chronic lung disease status in our cohort were based on community prescribing data as per ***Supplementary table 5***. Incident cases of endocarditis prescribed either anti-diabetic drugs or drugs for chronic lung disease with one year prior to hospitalization were defined as having the condition. Complete prescribing data was available from 2009.

Further information on the Prescribing Information System operational in Scotland is available at https://www.ndc.scot.nhs.uk/National-Datasets/data.asp?SubID=9

National microbiology register (Electronic Communication of Surveillance in Scotland [ECOSS])

The Scottish microbiology surveillance registry, or '*Electronic Communication of Surveillance in Scotland*' (ECOSS) as it is termed by NHS National Services Scotland, was used in the present study to provide individual patient-level data on positive blood culture results (from diagnostic microbiology laboratories within NHS Scotland health boards and national reference laboratories) related to incident cases of infective endocarditis identified from SMR01 between 2008 and 2014. ECOSS is part of NHS Scotland's Infection Intelligence Platform (IIP),[1,2] which was set-up in response to the UK's antimicrobial resistance (AMR) strategy (2013-2018) with the aim of providing "*better access to and use of surveillance data*".[3]

Data were first collected and recorded within ECOSS in 2007. The dataset is maintained by NHS National Services Scotland on behalf of Health Protection Scotland. ECOSS is updated monthly and, as of 2017, it contained approximately 29 million records of positive microbiology laboratory specimens from across Scotland.[1] It provides data for numerous national clinical and research activities, audit projects and Scottish Government reports, including: the identification of cases of severe infectious disease, infectious disease outbreaks and the evaluation of longer term trends in the incidence of laboratory-reported infections; surveillance of episodes of Clostridium difficile infections, Escherichia coli bacteremia, Staphylococcus aureus bacteremia and surgical site infections.[2] NHS National Services Scotland monitors the completeness and accuracy of ECOSS data through its 'Data Monitoring and Support Service'.[1] Further, NHS National Services Scotland routinely informs data users of any problems affecting the accuracy or assurance of these data.

In the present study, causative organisms were defined as those identified within 90 days on either side of the index admission date. Using this timeframe, 950 cases of infective endocarditis were associated with positive microbiological results.

Polymicrobial status was defined specifically is more than one causative organism was identified on the same culture date. If more than one causative organism was identified on differing dates, then the organism identified closest to the index admission date was assigned as the causative organism.

Near complete blood culture microbiology data were available from 2008. Three small Scottish laboratories did not provide complete data. These laboratories were as follows:

- Shetland (GIL:BAN) – no data for 2009-2011; for 2012 we only received two blood culture reports
- Western Isles (WES:LES) – no data for 2009-2010
- Orkney (ORK:BAL) – 2009 only one blood culture report received; no data for 2010

Overall these laboratories served <1.5% of the Scottish Population and would therefore have a negligible effect on the rates of non-positive blood cultures observed.

More information on the ECOSS data system is available at https://www.hps.scot.nhs.uk/data/

Approvals for use of data

Access to the data was approved by the NHS Scotland Public Benefit and Privacy Panel and in accordance with the Declaration of Helsinki. As the analysis used routinely collected and anonymized data, individual patient consent was not sought.

Supplementary text 2: ICD-9 and ICD-10 code identifiers employed to identify cases of infective endocarditis from SMR01 dataset

Co-morbidity	Relevant ICD codes
Infective endocarditis	
ICD-9	421.1, 424.91, 424.90, 424.99
ICD-10	I33, I38, I39
Myocardial infarction	
ICD-9	413
ICD-10	I21, I22
Cerebrovascular disease	
ICD9	430 - 438
ICD10	I60-I69
Heart failure	
ICD-9	428
ICD-10	I50
Valve surgery	
OPCS	K04 - K12, K14, K17 - K34
Cardiac device	
OPCS	K59 - K61

Supplementary text 3: Validation of SMR01 ICD-9 and ICD-10 coding for diagnosis and microbiology of infective endocarditis

Electronic hospital records of 396 episodes of suspected infective endocarditis dating from a 5-year period (2014-2018) were manually reviewed by two authors (PG and JH) as part of the validation exercise. The electronic records were reviewed to determine if the diagnosis of infective endocarditis was accurate.

SMR01 diagnostic code position	Positive predictive value, % (95% CI)
Main condition only (1)	97.1 (95.0 to 99.0)
Main condition and second diagnostic code position (1-2)	88.6 (84.7 to 92.5)
Main condition, second and third diagnostic code positions (1-3)	79.6 (75.7 to 83.5)
Any diagnostic code position (1-6)	67.9 (64.0 to 71.8)

Thereafter, electronic hospital records of 200 episodes of suspected infective endocarditis with a diagnostic code position of 1-3 and 168 episodes of suspected infective endocarditis with a diagnostic code position of 1-2 were reviewed in order to determine if blood cultures had been sent within 6 months of the index diagnosis from the admitting hospital.

SMR01 diagnostic code position	Overall blood cultures sent, n (%)
Main condition and second diagnostic code position (1-2)	147 (87.5)
SMR01 diagnostic code position	**Organism grown in blood cultures, n (%)**
Main condition and second diagnostic code position (1-2)	89 (52.9)

Clinical definition of infective endocarditis in our validation exercise

Although the Modified Duke Criteria (MDC) represent the 'gold standard' for defining cases of infective endocarditis, we were unable to employ the MDC reliably in our validation exercise. This was partly because the vast majority of clinicians did not reference the MDC in their documentation. Further, the presence or absence of key physical exam findings relevant to the minor criteria (e.g. vascular or immunologic phenomena) were frequently not

documented in patient records. After careful consideration of the impact of these missing data and the potential for introducing significant bias if we persisted with the MDC to define cases of infective endocarditis, our research team elected to employ a more pragmatic approach in the definition of infective endocarditis from electronic clinical records. The definition to define endocarditis has been summarised below.

Definition

True IE: Clinician diagnosis of IE documented in patient notes **and** patient treated as IE.
No IE: No clinician diagnosis of IE documented in patient notes **and/or** patient not treated as IE.

As mentioned above our validation work included all local cases of infective endocarditis from 2014 until 2018 (n=396). Of these, infective endocarditis was the first or second diagnostic code in 67% (264/396) of hospitalizations, and the first diagnostic code in 53% (208/396) of hospitalizations during this period. Confirming infective endocarditis based on the above definition and a diagnostic code position of one or two provided an overall positive predictive value of 88.6%. The table below summarises our validation work stratified by clinician adjudicated diagnosis of infective endocarditis and diagnostic position:

Certainty of infective endocarditis (IE) diagnosis	SMR01 diagnostic code position 1, n (%)	SMR01 diagnostic code positions 1 and 2, n (%)
True IE	202/208 (97.1%)	234/264 (88.6%)
No IE	6/208 (2.8%)	30/264 (11.4%)

Supplementary text 4: Description of 5 year lookback period and calculation of person-time

Lookback

The schematic below demonstrates an example of how the 5-year lookback period was employed in the period between 2000 and 2015 (inclusive) to identify incident events of infective endocarditis in three exemplar patients (patients A, B and C). The total incident count for each year is shown in the final column. Where a patient has been admitted with an episode of infective endocarditis, a '1' appears in the 'Admission' column. If no infective endocarditis event has occurred in the 5-years prior (i.e. the 'lookback' period, as indicated by the light grey shading), then the event is considered an incident event and a '1' will also appear in the 'Incident' column.

Year	Patient A		Patient B		Patient C		Total incident events
	Admission	Incident	Admission	Incident	Admission	Incident	
2000	0	0	0	0	0	0	**0**
2001	0	0	0	0	0	0	**0**
2002	0	0	0	0	0	0	**0**
2003	0	0	0	0	0	0	**0**
2004	0	0	0	0	0	0	**0**
2005	1	1	0	0	1	1	**2**
2006	1	0	1	1	0	0	**1**
2007	0	0	0	0	1	0	**0**
2008	0	0	0	0	0	0	**0**
2009	1	0	0	0	0	0	**0**
2010	0	0	0	0	0	0	**0**
2011	0	0	0	0	0	0	**0**
2012	0	0	0	0	0	0	**0**
2013	0	0	0	0	1	1	**1**
2014	0	0	0	0	0	0	**0**
2015	1	1	1	1	1	0	**2**

Person-time calculation

The schematic below demonstrates an example across three patients on how the person-time was calculated.

Year	POP	P1	P2	P3	PT
2004	190	0	1	1	189
2005	190	0	1	1	189
2006	190	0	1	0	188
2007	190	0	1	0	188
2008	190	0	1	0	188
2009	190	1	1	0	189
2010	185	1	1	0	184
2011	185	1	0	1	184
2012	185	1	0	1	184
2013	185	1	0	1	184
2014	185	1	0	1	184

POP refers to the mid-year estimate for the population (based on National Records Scotland census data and mid-year estimation modelling). P1, P2 and P3 refers to the person-time for each of the 3 patients with incident infective endocarditis. Patient 1 had an admission in 2004, they were not eligible to have another incident event within 5 years, and so the person-time for each of these periods is removed. Patient 2 had an incident event in 2011 and so only contributed 7 person-years. Patient 3 had an event in 2006 which was not incident, and as a consequence did not contribute to the period from 2006 to 2010 (inclusive).

The person-time for each year, within each stratum, is therefore calculated as follows:
$PT = POP - N + p1 + p2 + p3 + ...pn$ where N refers to the total number of individuals with incident infective endocarditis (in the above example, N would be equal to 3 as there are 3 patients).

Supplementary text 5: Use of ATC coding to determine comorbidity status

Comorbidity	Relevant class of drug (British National Formulary 62)	Chapter and section in the British National Formulary
Chronic respiratory disease	Respiratory system: all drugs	Chapter 3
Diabetes mellitus	Endocrine system: drugs used in diabetes	Chapter 6, section 6.1

Supplementary text 6: Details of interrupted time series analysis

To evaluate any change in the incidence of infective endocarditis before and after introduction of guidelines on antibiotic prophylaxis published by the National Institute of Health and Care Excellence, an interrupted time series analysis model was created.

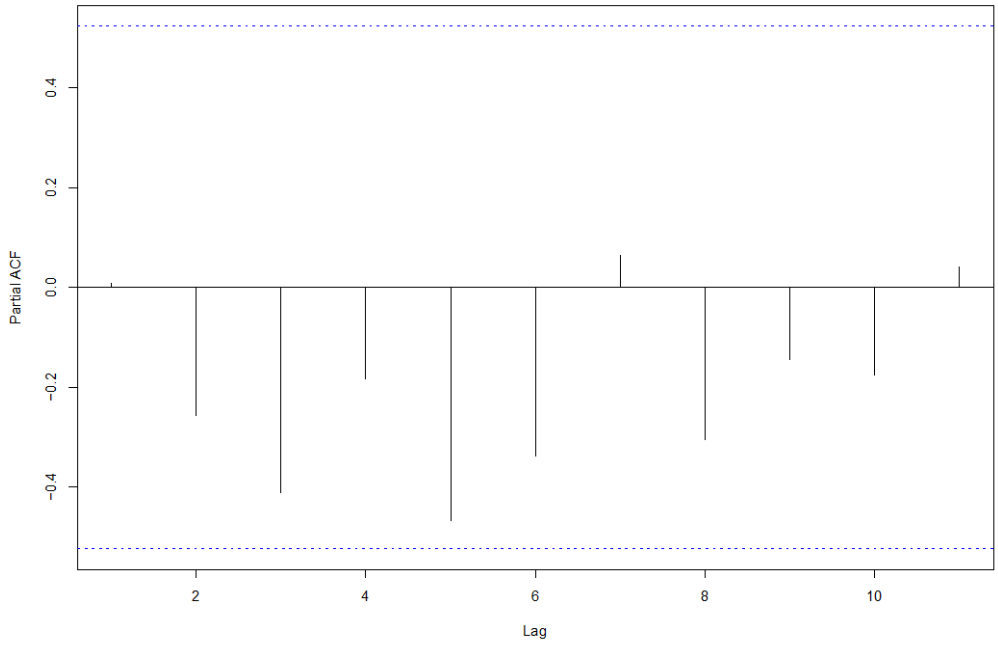
We chose a step-change model. A Poisson model was used as we were predicting count data. We modelled the count data directly (rather than the rate which doesn't follow a Poisson distribution), using the person-time (log transformed) as an offset variable in order to transform back to rates. In order to account for overdispersion we used a quasipoisson model (allowing the variance to be proportional rather than equal to the mean).

The following model was created with corresponding output:

model <- glm(count ~ offset(log(person_time)) + guidelines + year + guidelines*year, family=quasi-poisson, data)

Term	estimate	std.error	statistic	p-value
(Intercept)	-6.7862	25.2561	-0.2687	0.794
Guidelines	0.3997	34.9581	0.0114	0.991
Year	-0.0014	0.0126	-0.1082	0.916
Guidelines*Year	-0.0002	0.0174	-0.0098	0.992

The plot below shows no auto correlation removing the linear dependence of the lags using the partial autocorrelation function in the stats package in R Version 3·5·1 (Vienna, Austria):



Supplementary tables

Supplementary table 1: Baseline characteristics and short- and long-term outcomes stratified by single calendar years from 2008 to 2014

	Single-year groups						
	2008	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**
Number of patients, n	**340**	**311**	**317**	**312**	**315**	**311**	**361**
Age, years	66.2 (17.0)	66.8 (16.9)	65.9 (17.6)	67.5 (18.4)	66.5 (17.1)	67.7 (18.2)	65.4 (18.5)
Women, n (%)	167 (49.1)	142 (45.7)	144 (45.4)	151 (48.4)	151 (47.9)	160 (51.4)	162 (44.9)
Scottish index of multiple deprivation (SIMD) index, n (%)							
Rank 1 (most deprived)	80 (23.5)	82 (26.5)	72 (22.7)	69 (22.4)	66 (21.2)	72 (23.3)	86 (24.0)
Rank 2	71 (20.9)	73 (23.5)	65 (20.5)	79 (25.6)	82 (26.3)	72 (23.3)	78 (21.7)
Rank 3	77 (22.6)	61 (19.7)	68 (21.5)	64 (20.8)	59 (18.9)	50 (16.2)	78 (21.7)
Rank 4	62 (18.2)	50 (16.1)	64 (20.2)	47 (15.3)	47 (15.1)	58 (18.8)	58 (16.2)
Rank 5 (least deprived)	50 (14.7)	44 (14.2)	48 (15.1)	49 (15.9)	58 (18.6)	57 (18.4)	59 (16.4)
Previous medical conditions / interventions							
Myocardial infarction, n (%)	15 (4.4)	18 (5.8)	16 (5.0)	21 (6.7)	14 (4.4)	14 (4.5)	15 (4.2)
Cerebrovascular disease, n (%)	18 (5.3)	19 (6.1)	16 (5.0)	15 (4.8)	14 (3.4)	17 (5.5)	13 (3.6)
Heart failure hospitalization, n (%)	39 (11.5)	46 (14.8)	35 (11.0)	45 (14.4)	31 (9.8)	32 (10.3)	30 (8.3)
Cardiac device, n (%)	< 5	6 (1.9)	10 (3.2)	10 (3.2)	9 (2.9)	8 (2.6)	11 (3.0)
Cardiac valvular surgery, n (%)	15 (4.4)	26 (8.4)	35 (11.0)	29 (9.3)	22 (7.0)	22 (7.1)	22 (6.1)
Chronic respiratory disease, n (%)	-	42 (23.1)	69 (21.8)	51 (16.3)	56 (17.8)	51 (16.4)	65 (18.0)
Diabetes mellitus, n (%)	-	26 (14.3)	38 (12.0)	39 (12.5)	50 (15.9)	41 (13.2)	55 (15.2)
Outcomes at 30 days							
All-cause death, n (%)	48 (14.1)	30 (9.6)	51 (16.1)	54 (17.3)	39 (12.4)	32 (10.3)	47 (13.0)
Heart failure hospitalization, n (%)	20 (5.9)	20 (6.4)	18 (5.7)	14 (4.5)	13 (4.1)	17 (5.5)	12 (3.3)
Valve surgery, n (%)	20 (5.9)	15 (4.8)	20 (6.3)	15 (4.8)	12 (3.8)	17 (5.5)	22 (6.1)
Outcomes at 1 year							
All-cause death, n (%)	114 (33.5)	84 (27.0)	99 (31.2)	96 (30.8)	97 (30.8)	98 (31.5)	110 (30.5)
Heart failure hospitalization, n (%)	42 (12.4)	42 (13.5)	35 (11.0)	35 (11.2)	33 (10.5)	29 (9.3)	26 (7.2)
Valve surgery, n (%)	48 (14.1)	43 (13.8)	49 (15.5)	31 (9.9)	29 (9.2)	34 (10.9)	38 (10.5)

Supplementary table 2: Count data and estimated incidence rate per 100,000 stratified by year and sex

Year	Number of cases, n			Estimated crude incidence rate per 100,000								
	Overall	Males	Females	Overall	Lower 95% CI	Upper 95% CI	Males	Lower 95% CI	Upper 95% CI	Females	Lower 95% CI	Upper 95% CI
1990	201	100	101	5.34	4.80	5.94	5.62	4.87	6.48	5.28	4.54	6.15
1991	225	106	119	6.46	6.05	6.89	6.26	5.71	6.87	6.62	6.03	7.28
1992	318	130	188	7.53	7.08	8.02	6.91	6.34	7.53	7.95	7.29	8.66
1993	305	135	170	8.28	7.80	8.79	7.49	6.90	8.14	8.84	8.14	9.59
1994	330	137	193	8.59	8.13	9.08	7.98	7.39	8.63	9.09	8.41	9.82
1995	333	165	168	8.63	8.14	9.14	8.37	7.75	9.05	8.90	8.22	9.64
1996	326	143	183	8.58	8.11	9.07	8.63	8.01	9.31	8.59	7.94	9.29
1997	314	156	158	8.51	8.05	9.00	8.71	8.08	9.38	8.37	7.73	9.06
1998	326	164	162	8.40	7.93	8.90	8.55	7.92	9.24	8.25	7.60	8.95
1999	330	152	178	8.21	7.76	8.68	8.24	7.63	8.89	8.15	7.52	8.82
2000	291	130	161	7.94	7.49	8.41	7.87	7.28	8.51	7.98	7.35	8.66
2001	291	138	153	7.66	7.22	8.13	7.56	6.99	8.19	7.75	7.13	8.42
2002	278	131	147	7.41	6.99	7.86	7.35	6.79	7.95	7.48	6.88	8.12
2003	303	144	159	7.22	6.80	7.67	7.24	6.68	7.84	7.23	6.64	7.88
2004	272	130	142	7.11	6.70	7.56	7.24	6.68	7.84	7.06	6.48	7.69
2005	264	119	145	7.14	6.73	7.57	7.41	6.86	8.01	6.97	6.41	7.59
2006	282	153	129	7.32	6.89	7.77	7.77	7.19	8.40	6.96	6.38	7.59
2007	314	160	154	7.60	7.18	8.06	8.24	7.65	8.88	6.98	6.42	7.60
2008	332	169	163	7.83	7.40	8.29	8.61	8.00	9.27	6.99	6.42	7.61
2009	302	164	138	7.84	7.39	8.31	8.66	8.04	9.33	6.95	6.37	7.58
2010	314	171	143	7.61	7.20	8.05	8.40	7.81	9.03	6.87	6.32	7.47
2011	302	155	147	7.36	6.94	7.81	8.08	7.49	8.72	6.82	6.25	7.44
2012	307	160	147	7.32	6.89	7.78	8.00	7.40	8.64	6.87	6.29	7.51
2013	302	144	158	7.60	7.19	8.05	8.29	7.69	8.94	7.05	6.47	7.68
2014	351	193	158	8.14	7.47	8.87	8.88	7.93	9.94	7.30	6.41	8.31

Supplementary table 3: Count data and estimated incidence rate per 100,000 stratified by year and age group

Year	Estimated crude incidence rate per 100,000											
	20-39 years			40-59 years			60-79 years			≥80 years		
	Rate per 100,000	Lower 95% CI	Upper 95% CI	Rate per 100,000	Lower 95% CI	Upper 95% CI	Rate per 100,000	Lower 95% CI	Upper 95% CI	Rate per 100,000	Lower 95% CI	Upper 95% CI
1990	2.27	2.04	2.51	4.70	3.93	5.63	11.50	10.01	13.21	17.66	13.36	23.32
1991	2.27	2.06	2.50	5.03	4.46	5.69	13.56	12.37	14.87	20.06	16.22	24.80
1992	2.28	2.08	2.49	5.35	4.80	5.96	15.78	14.59	17.08	22.55	18.99	26.78
1993	2.28	2.10	2.48	5.58	5.02	6.20	17.87	16.58	19.25	24.89	21.40	28.94
1994	2.29	2.11	2.47	5.67	5.11	6.28	19.48	18.14	20.91	26.90	23.35	30.98
1995	2.29	2.13	2.47	5.57	5.02	6.18	20.39	19.00	21.88	28.56	24.89	32.76
1996	2.30	2.14	2.46	5.33	4.81	5.91	20.56	19.19	22.02	29.93	26.17	34.22
1997	2.30	2.16	2.45	5.02	4.52	5.57	20.10	18.76	21.54	31.03	27.20	35.40
1998	2.31	2.17	2.45	4.72	4.24	5.25	19.21	17.90	20.62	31.85	27.97	36.26
1999	2.31	2.18	2.45	4.46	4.01	4.97	18.09	16.85	19.42	32.34	28.47	36.74
2000	2.32	2.19	2.45	4.27	3.82	4.76	16.94	15.74	18.22	32.54	28.69	36.92
2001	2.32	2.20	2.45	4.10	3.67	4.58	15.92	14.77	17.16	32.52	28.70	36.84
2002	2.33	2.20	2.45	3.96	3.55	4.43	15.17	14.06	16.35	32.35	28.59	36.59
2003	2.33	2.21	2.46	3.86	3.45	4.32	14.74	13.65	15.92	32.09	28.38	36.29
2004	2.34	2.21	2.47	3.81	3.41	4.26	14.66	13.58	15.82	31.82	28.16	35.95
2005	2.34	2.21	2.48	3.83	3.43	4.27	14.84	13.76	16.00	31.63	28.02	35.71
2006	2.35	2.20	2.50	3.89	3.49	4.35	15.13	14.03	16.32	31.65	28.04	35.73
2007	2.35	2.20	2.51	3.97	3.56	4.42	15.34	14.24	16.53	31.94	28.32	36.02
2008	2.36	2.19	2.53	3.99	3.58	4.45	15.28	14.19	16.46	32.48	28.82	36.60
2009	2.36	2.19	2.55	3.95	3.54	4.41	14.91	13.82	16.07	33.18	29.46	37.37
2010	2.37	2.18	2.57	3.89	3.49	4.34	14.31	13.27	15.43	33.96	30.22	38.15
2011	2.37	2.17	2.59	3.89	3.48	4.34	13.68	12.66	14.79	34.78	31.00	39.03
2012	2.38	2.17	2.61	4.00	3.58	4.46	13.17	12.17	14.25	35.69	31.72	40.17
2013	2.38	2.16	2.63	4.24	3.78	4.77	12.82	11.77	13.97	36.72	32.06	42.07
2014	2.39	2.15	2.65	4.59	3.88	5.43	12.58	11.09	14.27	37.85	31.51	45.46

Supplementary table 4: Model coefficients from generalized additive model evaluating all-cause mortality by calendar year, adjusted for age and comorbidity

	Estimate	Standard error	z value	Odds ratio	Lower 95% CI	Upper 95% CI	p-value
(Intercept)	-0.50	0.10	-4.90	-	-	-	-
Female sex	-0.16	0.05	-3.03	0.85	0.75	0.96	0.002
Deprivation (per unit increment)	-0.09	0.02	-4.69	0.92	0.88	0.95	<0.001
Heart failure hospitalization	0.74	0.07	10.75	2.09	1.96	2.22	<0.001
Myocardial infarction	0.08	0.12	0.66	1.08	0.85	1.31	0.512
Cerebrovascular disease	0.25	0.11	2.27	1.28	1.07	1.49	0.023

Estimates of non-linear smooth functions	Estimated degrees of freedom	Chi-squared	p-value
s(year)	1.01	4.48	0.035
s(age_years)	5.64	486.50	<0.001

Supplementary table 5: Predicted one-year mortality in women and men from the generalized additive models

YEAR	WOMEN			MEN		
	Probability	**95% LL**	**95% UL**	**Probability**	**95% LL**	**95% UL**
1990	27.32	24.62	30.21	30.66	27.71	33.78
1991	27.17	24.54	29.96	30.50	27.64	33.51
1992	27.01	24.46	29.72	30.33	27.57	33.24
1993	26.86	24.38	29.48	30.16	27.48	32.98
1994	26.70	24.29	29.26	29.99	27.39	32.73
1995	26.55	24.19	29.04	29.83	27.30	32.49
1996	26.39	24.09	28.83	29.66	27.20	32.26
1997	26.24	23.98	28.63	29.50	27.09	32.03
1998	26.09	23.86	28.44	29.33	26.97	31.82
1999	25.93	23.73	28.26	29.17	26.84	31.61
2000	25.78	23.60	28.09	29.01	26.71	31.42
2001	25.63	23.45	27.93	28.85	26.56	31.24
2002	25.48	23.31	27.78	28.68	26.41	31.07
2003	25.33	23.15	27.64	28.52	26.25	30.90
2004	25.18	22.99	27.51	28.36	26.08	30.75
2005	25.03	22.82	27.39	28.20	25.91	30.61
2006	24.88	22.64	27.27	28.04	25.72	30.48
2007	24.74	22.46	27.17	27.88	25.53	30.36
2008	24.59	22.27	27.07	27.72	25.33	30.24
2009	24.44	22.08	26.97	27.56	25.13	30.14
2010	24.30	21.88	26.89	27.40	24.92	30.04
2011	24.15	21.68	26.81	27.25	24.70	29.95
2012	24.01	21.47	26.73	27.09	24.49	29.86
2013	23.86	21.27	26.66	26.93	24.26	29.79
2014	23.72	21.06	26.60	26.78	24.03	29.71

Supplementary table 6: Logistic regression model coefficients and standard errors with mortality at 30 days as the primary outcome.

	Estimate	Std. Error	z value	Pr (>|z|)
(Intercept)	-2.66	0.31	-8.57	<0.001
Baseline characteristics				
Age	0.02	0.01	1.31	0.191
Sex	0.08	0.15	0.51	0.612
Deprivation (per unit increment)	0.02	0.05	0.36	0.720
Age:sex interaction	<0.001	0.009	0.08	0.936
Co-morbidities				
Heart failure hospitalization	0.59	0.19	3.05	0.002
Myocardial infarction	0.33	0.28	1.18	0.238
Cerebrovascular disease	0.18	0.30	0.60	0.546
Chronic lung disease	0.13	0.18	0.72	0.470
Diabetes mellitus	-0.21	0.21	-0.98	0.328
Microbiology				
Enterococcus sp.	0.65	0.35	1.86	0.06
Polymicrobial/other	0.24	0.36	0.66	0.511
Staphylococcus aureus	1.40	0.20	7.17	<0.001
Coagulase negative staphylococci	1.26	0.28	4.45	<0.001
Streptococcus sp.	0.65	0.21	3.15	0.002

Supplementary table 7: Logistic regression model coefficients and standard errors with mortality at 1 year as the primary outcome.

	Estimate	Std. Error	z value	Pr (>|z|)
(Intercept)	-1.18	0.23	-5.04	<0.001
Baseline characteristics				
Age (per 10 years)	0.04	0.01	3.69	<0.001
Sex	-0.14	0.12	-1.16	0.247
Deprivation (per unit increment)	-0.04	0.04	-1.08	0.282
Age:sex interaction	-0.001	0.007	-0.14	0.889
Co-morbidities				
Heart failure hospitalization	0.87	0.16	5.38	<0.001
Myocardial infarction	0.42	0.23	1.82	0.069
Cerebrovascular disease	-0.21	0.25	-0.81	0.418
Chronic lung disease	0.04	0.14	0.30	0.765
Diabetes mellitus	0.07	0.16	0.43	0.671
Microbiology				
Enterococcus sp.	1.23	0.26	4.70	<0.001
Polymicrobial/other	0.71	0.25	2.89	0.004
Staphylococcus aureus	1.47	0.17	8.69	<0.001
Coagulase negative staphylococci	1.03	0.25	4.15	<0.001
Streptococcus sp.	0.51	0.16	3.10	0.002

Supplementary References

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